NIAID

National Institute of Allergy and Infectious Diseases

Profile

Fiscal Year 2000

National Institutes of Health

U.S. Department of Health and Human Services

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June 2001
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This is a stylized representation of an antibody, a protein made by the body's immune system cells to protect it against invading foreign substances.

For additional information, see our web site at
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Introduction

The National Institute of Allergy and Infectious Diseases (NIAID) conducts and supports scientific research on infectious and immunologic diseases. The goals of this research are to delineate pathogenesis, improve diagnosis and treatment, and develop vaccines to prevent these diseases, many of which significantly affect public health. To accomplish its goals, NIAID carries out a wide range of basic, applied, and clinical investigations within its own laboratories and provides research grant, contract, and cooperative agreement support to scientists at universities and other research institutions throughout the country and the world.

The NIAID research program is predicated on the view that we live in an interconnected global community. Because of the enormous volume of international travel and trade, we cannot separate the health problems of the United States from those of the rest of the world. Clearly, it is naive to think that we are somehow isolated from diseases that are public health challenges elsewhere. As a nation, our interest in global health stems from both humanitarian concerns and what has been called "enlightened self-interest." In addition to our obligation to ameliorate human suffering wherever possible, history tells us that healthy, stable countries make strong allies and trading partners. Conversely, poor health status can have a profound negative impact on social and economic development, and can contribute to political instability.

For example, the current AIDS crisis in sub-Saharan Africa is dramatically affecting people in all age groups and lowering life expectancy, which affects workforce capabilities and reduces the growth potential of local enterprise. An estimated 36.1 million people worldwide are living with HIV/AIDS, a prevalence twofold higher than projected a decade ago.[1] The magnitude of the HIV/AIDS crisis is so great in some countries that it attracted the attention of the U.N. Security Council, which in January 2000 devoted an entire session to the impact of HIV/AIDS on peace and security in Africa. The development of a safe and effective vaccine for HIV infection remains the ultimate goal in AIDS research, and many promising candidate vaccines are in various stages of preclinical and clinical development. NIAID will continue to pursue the mysteries surrounding HIV infection and AIDS by supporting HIV/AIDS research through its multiple research programs and multicenter clinical trials networks.

Basic research in immunology and microbiology is yielding promising candidates for vaccine development. For example, the construction of influenza A virus from its individual DNA building blocks has reduced many of the hurdles impeding development of an improved vaccine for this widespread disease. In addition, scientists gained a greater understanding of the role of vector organisms in the infectivity of *Plasmodium falciparum*, the organism that causes malaria, and *Leishmania major*, the parasite that causes leishmaniasis. These advances, and others in the understanding of HIV and the hepatitis C virus, may lead to effective vaccines for these infections. NIAID also leads basic and clinical research efforts in the development of safe and effective vaccines for the prevention of a variety of other infectious diseases.

Worldwide, infectious diseases are the second leading cause of death, responsible for 25 percent of deaths.[2] New infectious pathogens continue to emerge throughout the world, from Ebola virus in Africa to West Nile virus in the United States. The documentation in New York of West Nile

[1] UNAIDS. AIDS epidemic update: December 2000. Joint United Nations Programme on HIV/AIDS, World Health Organizations, 2000.

[2] WHO. Removing Obstacles to Health Development. WHO Report on Infectious Diseases. (1999).

encephalitis, a disease never before seen in the Western Hemisphere, emphasized the importance of research into global health. Diseases also are emerging in local areas. Organisms that are resistant to standard treatments, such as multi-drug-resistant *Mycobacterium tuberculosis* and antibiotic-resistant *Staphylococcus aureus*, are of concern, putting children, the elderly, and immuno-compromised populations at particular risk of developing life-threatening infections.

Research on the immune system has resulted in a wealth of new information and growth in our understanding of autoimmune diseases and immune tolerance. This knowledge may offer new means to confront many important diseases, such as type 1 diabetes and multiple sclerosis. Despite considerable gaps in knowledge, researchers are gaining an understanding of the complexities of immune activation and regulation within the physiological framework of the whole organism. As we enter the next century, these advances provide a solid foundation for translating basic research into clinical applications.

New opportunities for the study of immunology and infectious diseases derive from technologies developed within the past 5 years. Progress in DNA sequencing, combined with advances in computer programming, has dramatically accelerated the pace of genome sequencing. The ability to rapidly sequence a pathogen's genomes, combined with sophisticated new means of genome analysis, such as DNA chips and other microarray technologies, is speeding the development of new diagnostics, treatments, and prevention strategies. In addition, investigators now can use computer models, x-ray crystallography, combinatorial chemistry, and robotics to rationally design drugs. These technologies promise to accelerate the pace of discovery.

NIAID maintains a strong commitment to basic research and to clinical studies on other infectious and immunologic diseases within its mission by continuing to conduct and support work on preventing and treating sexually transmitted diseases, asthma and allergies, and parasitic and fungal diseases; on diagnostics; on evaluation of antiviral drugs; and on transplantation immunology. NIAID also continues to provide support for research on international health issues and tropical medicine.

Profile describes the Institute's activities in these diverse but interrelated areas of basic research and clinical investigation and provides overviews of the major accomplishments and goals of the various scientific programs within the Institute. *Profile* also includes information on the organization and staff of NIAID, the Institute's budget and distribution of funding, and its extramural grants, contracts, and research training programs.

The United Nations, in the International Declaration of Health Rights, asserted that "The enjoyment of the highest attainable standard of health is one of the fundamental rights of every human being. It is not a privilege reserved for those with power, money or social standing." As NIAID faces the new millennium, we anticipate that our research efforts will result in new and improved vaccines, diagnostics, and treatments that will make "the highest attainable standard of health" a global reality.

/c/

Anthony S. Fauci, M.D.
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Contents

Council and Review Committees

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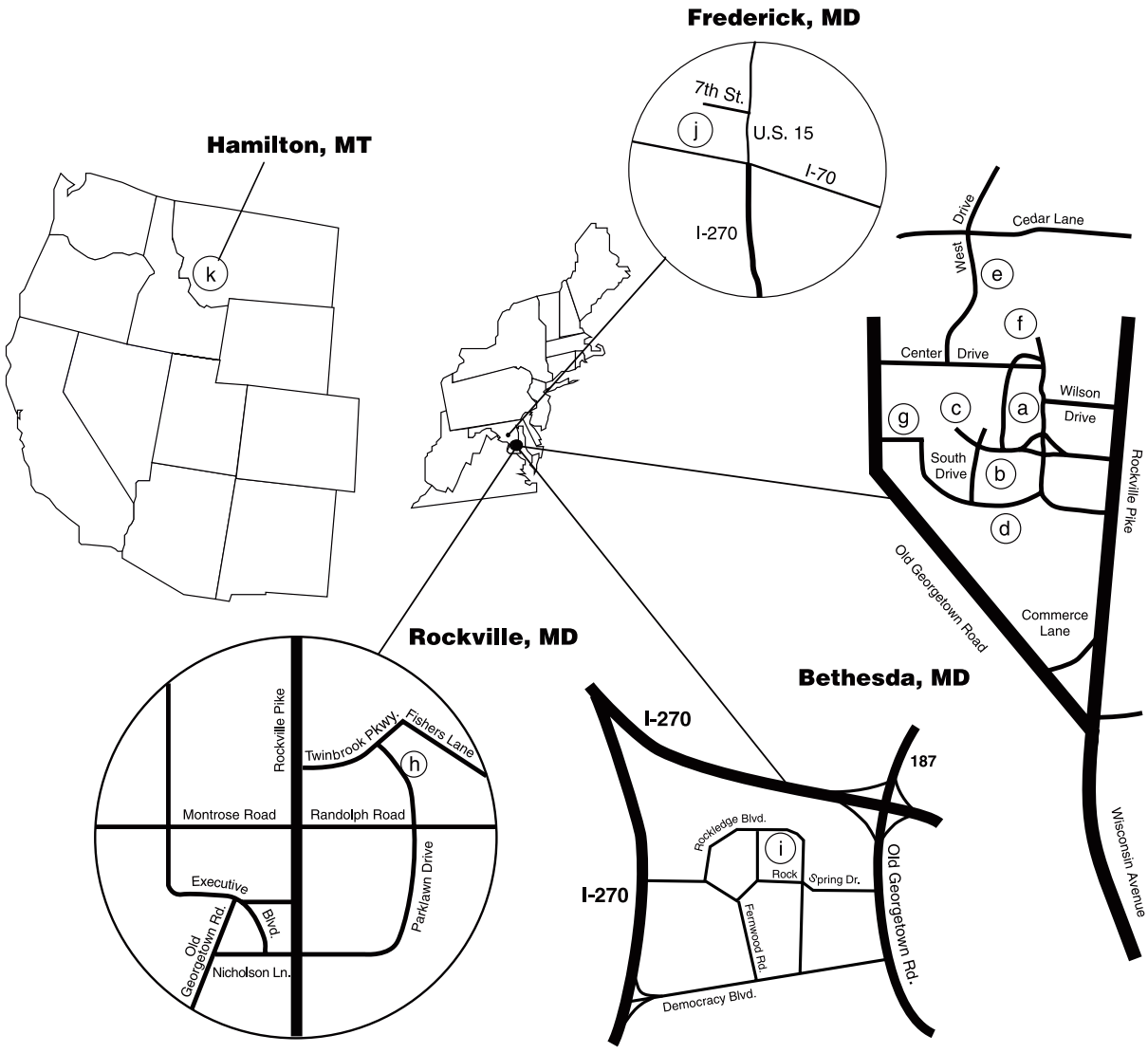

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Bethesda, MD 20892

e Building 15B-1
NIH Campus
9000 Rockville Pike
Bethesda, MD 20892

f Building 31
NIH Campus
9000 Rockville Pike
Bethesda, MD 20892

g Building 40/VRC
NIH Campus
9000 Rockville Pike
Bethesda, MD 20892

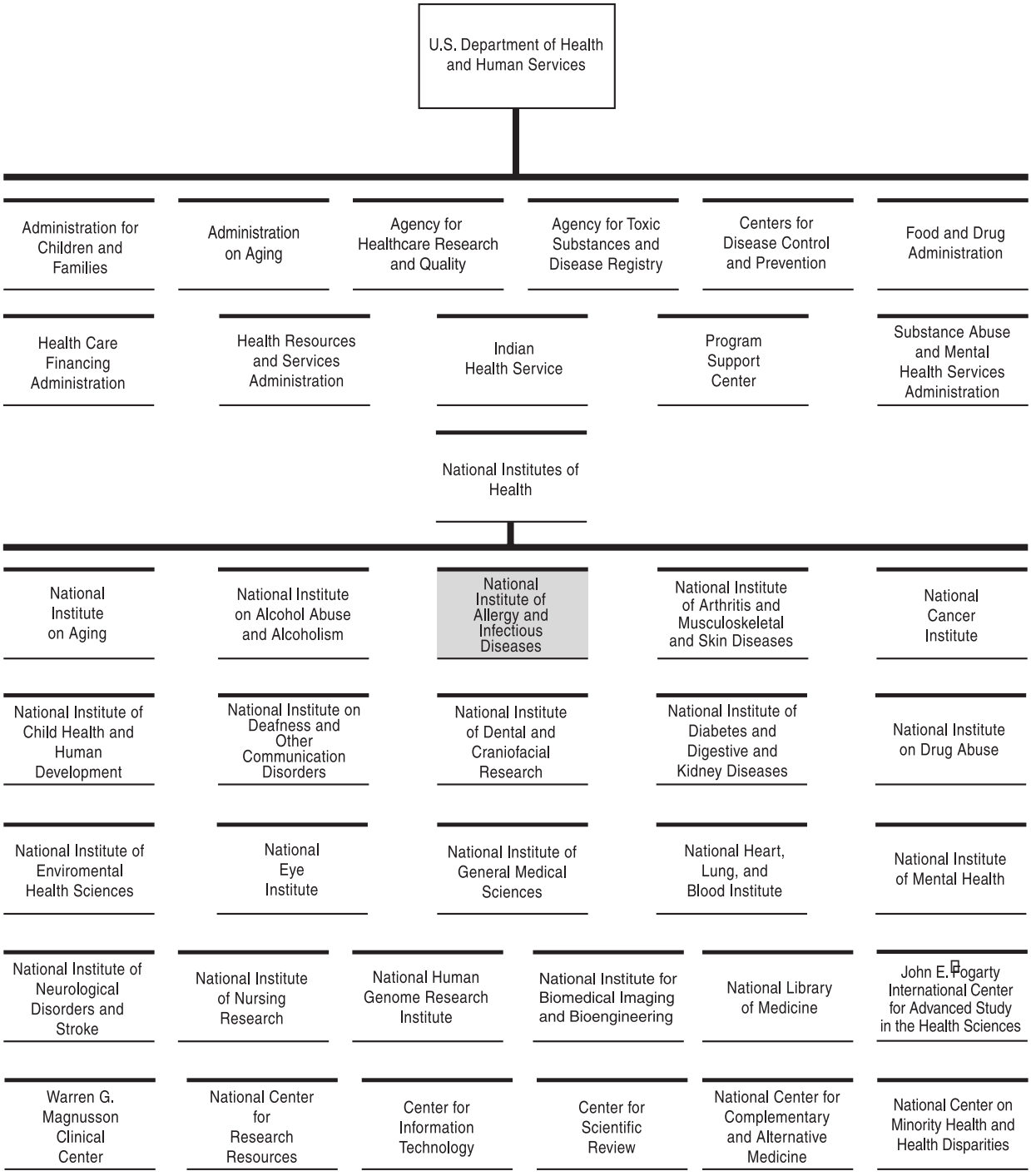
h Twinbrook II
12441 Parklawn Drive
Rockville, MD 20852

i Rockledge Building (6700 B)
6700 B Rockledge Drive
Bethesda, MD 20892

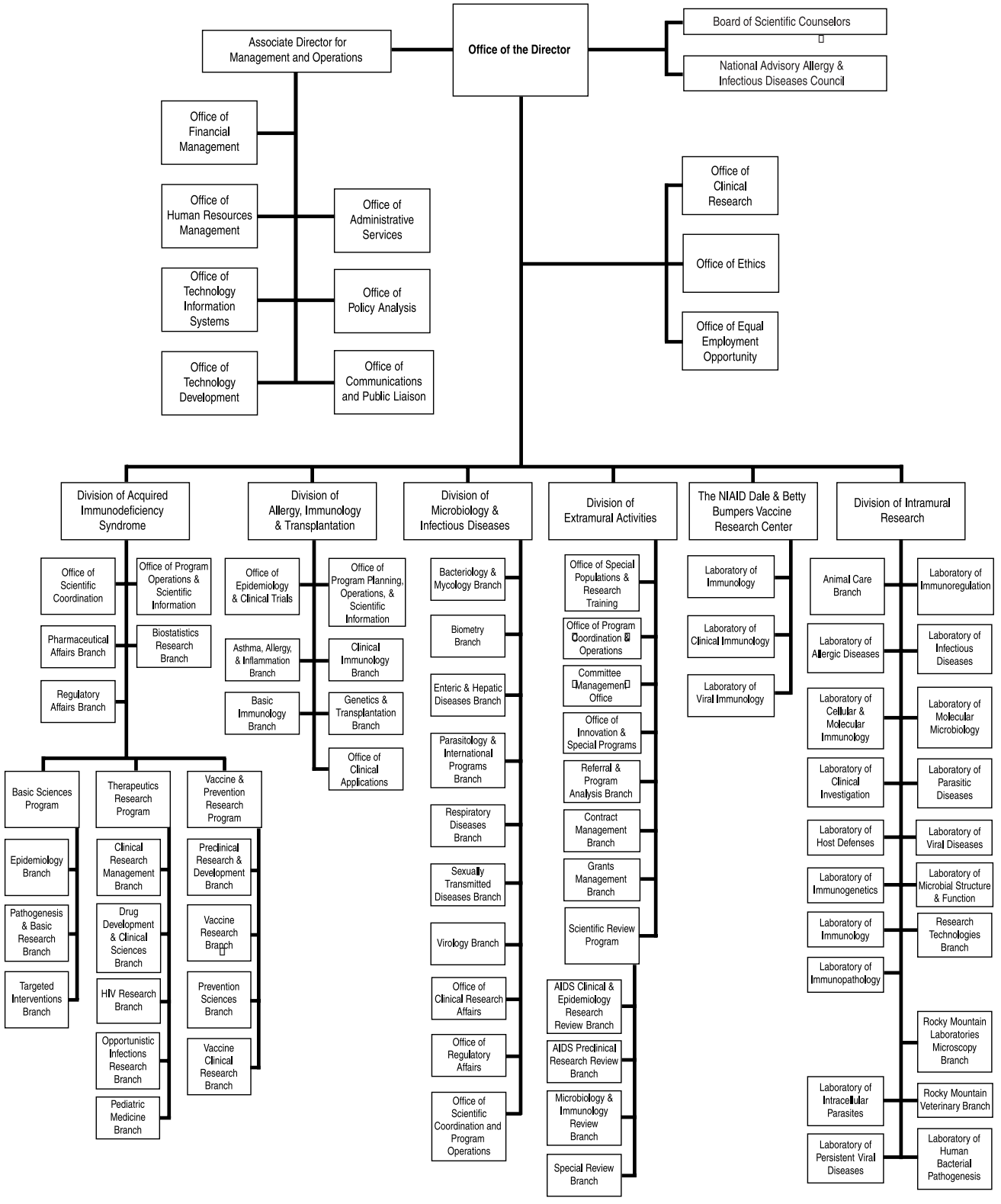
j Frederick Cancer Research and Development Center
Building 550
Ft. Detrick, MD 21701

k Rocky Mountain Laboratories
903 South Fourth Street
Hamilton, MT 59840

Location of NIAID in the U.S. Department of Health and Human Services



NIAID Organizational Chart



Note: The most up-to-date organizational chart is located on the World Wide Web at http://www.niaid.nih.gov/organization/default.htm.

NIAID Director

Anthony S. Fauci, M.D., became the Director of NIAID in 1984. He was born in Brooklyn, New York, and received his undergraduate degree from Holy Cross College in 1962 and his medical degree from Cornell University Medical College in 1966. He completed his internship and residency at The New York Hospital-Cornell Medical Center and joined NIAID in 1968 as a clinical associate in the Laboratory of Clinical Investigation (LCI). In 1974, he became Head of the Clinical Physiology Section, LCI, and in 1977, he was appointed Deputy Clinical Director of NIAID. In 1980, Dr. Fauci became Chief of the Laboratory of Immunoregulation, a post he continues to hold.

Dr. Fauci has made many contributions to basic and clinical research on the pathogenesis and treatment of immune-mediated diseases. He is an internationally renowned scientist and has pioneered the field of human immunoregulation by making a number of basic scientific observations that serve as the basis for current understanding of the regulation of the human immune response. In addition, Dr. Fauci is widely recognized for delineating the precise mechanisms whereby immunosuppressive agents modulate the human immune response. He has developed effective therapies for formerly fatal diseases such as polyarteritis nodosa, Wegener's granulomatosis, and lymphomatoid granulomatosis.

Dr. Fauci has made seminal contributions to the understanding of how the AIDS virus destroys the body's defenses, leading to its susceptibility to deadly infections. He has also delineated the mechanisms of induction of HIV expression by endogenous cytokines. Furthermore, he has been instrumental in developing strategies for the therapy and immune reconstitution of patients with this serious disease, as well as for a vaccine to prevent HIV infection. He continues to devote much of his research time to identifying the nature of the immunopathogenic mechanisms of HIV infection and the scope of the body's immune responses to the AIDS retrovirus.

During his career as a biomedical researcher, Dr. Fauci has authored, coauthored, or edited more than 1,000 scientific publications. He has served as a visiting professor at medical centers throughout the country, and has delivered many major lectures at institutions and conferences all over the world.

Dr. Fauci is a member of the prestigious National Academy of Sciences, the Royal Danish Academy of Science and Letters, the American Academy of Arts and Sciences, and the Institute of Medicine of the National Academy of Sciences, where he is a Council member. He is a member of many professional societies, including the American College of Physicians, the Infectious Diseases Society of America, the American Society for Clinical Investigation, the Association of American Physicians, and the American Academy of Allergy, Asthma and Immunology. He serves on a number of editorial boards and is an editor of *Harrison's Principles of Internal Medicine.* He has received numerous awards for his scientific accomplishments, including 22 honorary doctorate degrees.

Office of the Director

The Office of the Director (OD), NIAID, provides policy guidance, program development and evaluation, and overall operational and administrative coordination for the Institute. OD is the focal point of relationships with the Director of the National Institutes of Health (NIH), as well as with other Government agencies, Congress, professional societies, voluntary health agencies, and other public groups. OD's activities also include advising and guiding NIAID's key leaders on the principles, practices, laws, regulations, and policies of the Federal equal employment, affirmative action, civil rights, and minority programs.

Offices within OD provide critical management and administrative support to the Institute. For example, the Office of Policy Analysis provides overall planning and policy guidance and legislative outreach and support. This Office is responsible for Government Performance Results Act and Freedom of Information Act reporting. During fiscal year (FY) 2001, the Office coordinated a revision to NIAID's strategic plan, incorporating the Institute's crosscutting elements on health disparities that reflect the NIAID Health Disparities Strategic Plan.

The Office of Financial Management provides overall financial management and budget analysis to the Director and the Institute, as well as budget-related briefing materials for the Director's briefings with the Department, Office of Management and Budget, and Congress.

The Office of Technology Development administers the Institute's technology transfer activities regarding Cooperative Research and Development Agreements, Material Transfer Agreements, Clinical Trial Agreements, patents, royalties, and related matters.

The Office of Technology Information Systems manages local- and wide-area network support for NIAID. Moreover, the Office develops applications software and provides application support for NIAID computer databases. The Office also provides training, professional development, and consultative services.

The Office of Human Resources Management provides central human resource services for the executive staff, Institute management, employees, and applicants. These services encompass recruitment and staffing, position management and classification, pay and compensation, employee relations, and employee development.

The Office of Administrative Services helps NIAID staff members carry out their jobs by providing administrative and acquisition management services. These services include procurement, space management, and travel. This Office coordinates and oversees the Government ethics program within NIAID, develops internal controls in such areas as property accountability and financial monitoring, and coordinates and analyzes organizational changes.

NIAID meets an important part of its mission by conveying the results of its research programs to health professionals and the public. Through a variety of activities aimed at the media and public and professional audiences, the Office of Communications and Public Liaison provides information about the goals and results of NIAID's research programs. In addition to responding to more than 25,000 requests for information annually,

the Office plans educational and media campaigns; develops and disseminates brochures, fact sheets, press releases, and audiovisual products; and produces educational exhibits for national and regional meetings. The Office coordinates all the activities related to NIAID's homepage on the Internet.

The Office of Clinical Research manages and coordinates those NIAID research programs that use the Warren Grant Magnuson Clinical Center located on the NIH Bethesda campus. The Office promotes interactions and collaborations between intramural and extramural investigators and oversees NIAID's Institutional Review Board, which provides initial and continuing review of intramural clinical research protocols to protect the welfare of human subjects recruited to participate in biomedical or behavioral research. The Office provides any relevant information from NIAID's clinical research programs to the NIH community and other Government agencies, as well as to public and private organizations.

The Office of Equal Employment Opportunity is responsible for planning, implementing, evaluating, and monitoring programs and initiatives to increase the number of minorities, women, and people with disabilities in all scientific and administrative areas of the Institute. The Office also develops initiatives that further enhance biomedical research programs at historically black colleges and universities and at Hispanic-serving institutions, and coordinates all activities that implement NIH minority-assistance programs and objectives that also relate to the mission of NIAID.

The Office of Ethics provides advice to OD regarding conflict of interest of individuals involved in the conduct of biomedical research, including Government employees, advisory committee members, and non-Government employees such as peer reviewers or Data Safety Monitoring Board members. The Office also administers a comprehensive NIAID ethics program that reflects statutory responsibilities and integrity in service to the public.

Outreach Activities

The NIAID Office of Communications and Public Liaison (OCPL) is the focal point within the Institute for dissemination of research results to the media, health professionals, and the public. An important part of NIAID's mission, this activity includes producing and disseminating print, audiovisual, and Internet materials; exhibiting materials at professional and community meetings; sponsoring workshops and conferences for community health care providers and the public; and supporting demonstration and education research projects.

OCPL produces materials on topics ranging from allergic and immunologic diseases to AIDS and other sexually transmitted diseases. These materials include press releases, fact sheets, and booklets, which are distributed to more than 25,000 people who contact the Institute from all around the world each year. In addition, hundreds of thousands more download or request materials from the NIAID web site (http://www.niaid.nih.gov), which is now visited a million times each month.

The NIAID web site is a searchable site containing a wealth of information about NIAID's organization and research programs, as well as descriptions of NIAID's laboratories. For example, the Extramural Information Center includes program announcements, contact information for key personnel, and many other items of interest to current and potential grantees and contractors.

NIAID's Office of Policy Analysis (OPA) produced the NIAID Strategic Plan in FY 2000, which is also posted on the NIAID web site. This document describes broad-based Institute priorities that will guide NIAID programs, policies, and initiatives through the next 3 to 5 years. OPA published the executive summary, *NIAID: Planning for the 21st Century,* of which several hundred copies have been distributed to congressional offices, constituency groups, and others, as well as at scientific meetings.

OCPL is working with OPA to produce and distribute the *NIAID Strategic Plan for Addressing Health Disparities.* This report is also posted on the NIAID web site and will be distributed widely in FY 2001.

In addition, OCPL works with NIAID research programs to produce and distribute various reports. For example, NIAID's Division of Allergy, Immunology and Transplantation produced the NIH Autoimmune Diseases Coordinating Committee Report. This report contains information about research on autoimmune diseases that is being conducted and supported by several NIH Institutes as well as by private organizations. Autoimmune diseases include type 1 diabetes, rheumatoid arthritis, and systemic lupus erythematosus.

During FY 2000, Institute staff distributed materials to attendees at scientific and health-related meetings, including the American Academy of Allergy, Asthma, and Immunology; the American Public Health Association; the National Medical Association; the Infectious Diseases Society of America; the American Association for the Advancement of Science; the American Society for Microbiology; the National Conference on Blacks in Higher Education; the Society for the Advancement of Chicanos and Native Americans in Science; the U.S. Conference on HIV/AIDS; and others.

In FY 2000, OCPL began updating its very popular series of eight easy-to-read booklets on HIV/AIDS, which is also available in Spanish.

Research Planning

NIAID's annual planning process involves developing and selecting initiatives that solicit research applications in specific areas. The process includes a progression of decision-making events informed by a continuous stream of reviews, evaluations, and consultations. The two pillars of this process are the Summer Program Review (SPR) and the Winter Policy Retreat (WPR).

The objectives of the SPR include the following:

- Focus on broad scientific issues, opportunities, gaps, and directions;
- Identify the basis for the opportunities and/or gaps;
- Identify the relationship between the opportunities and/or gaps and the needs and/or special initiatives or priorities of the Congress, Administration, Department, or NIH Director;
- Propose approaches for responding to the newly identified opportunities and/or needs;
- Identify implications of changes in scientific and/or programmatic direction; and
- Prioritize newly identified opportunities and/or needs within the future budget year.

The planning process is further enriched during the WPR, where the objectives include the following:

- Identify major public health, scientific, legislative, and budget directions that will influence NIAID programs;
- Discuss the scientific framework for and priority of new and renewed future budget year programs in the context of the above factors; and
- Use this information to make decisions about activities to be initiated in the future budget year.

NIAID's planning process was cited as a model by the Institute of Medicine in its 1998 report, *Scientific Opportunities and Public Health Needs: Improving Priority Setting at the National Institutes of Health.*

Throughout the year, NIAID holds scientific workshops, blue ribbon panels, and program reviews to evaluate progress in the field and to determine future needs and opportunities. The NIAID Director and each division consult extensively with NIAID stakeholders; these consultations inform the development of initiatives addressed during the structured planning process. Areas of emphasis identified by the U.S. Department of Health and Human Services, the NIH, Congress, the White House, and others also help shape the Institute's decisions on whether to alter course or to initiate new activities.

Planning for initiatives begins 2 years in advance of the award year and is a multistep process. At each step in the process, the idea is reviewed and refined. First, a concept for an initiative is subjected to internal review during a retreat. Reviewed and prioritized concepts then are reviewed and cleared by the

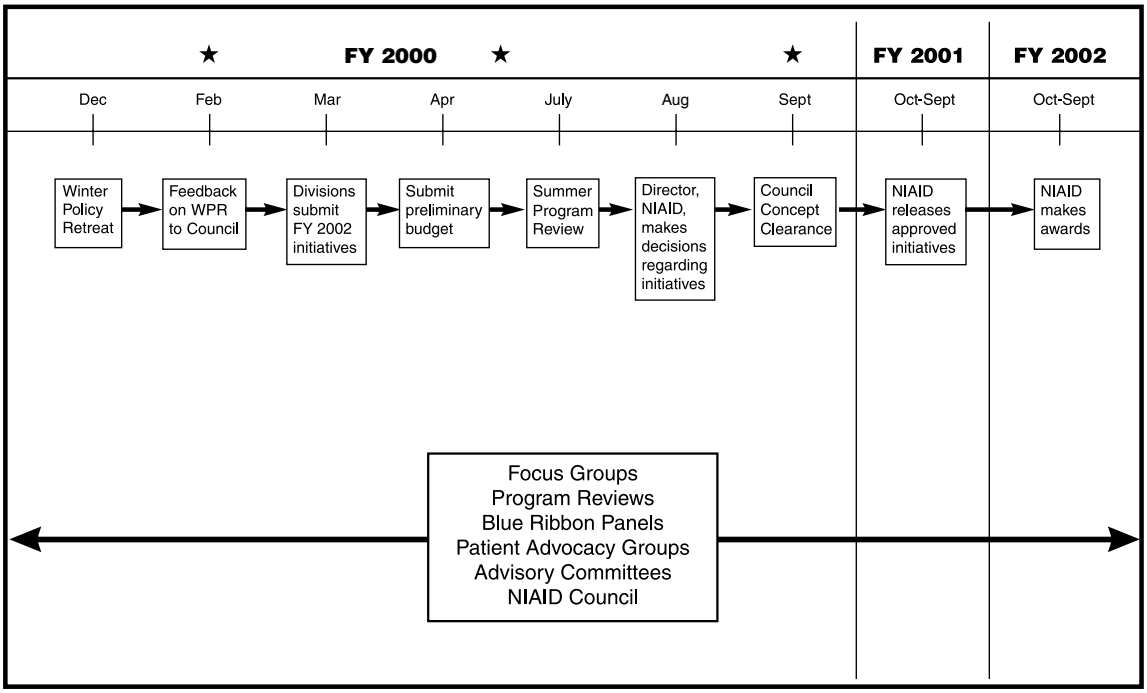
National Advisory Allergy and Infectious Diseases Council. The divisions then build on the chosen concepts by providing the detailed information required for program announcements, requests for applications, or requests for proposals. The proposed initiatives are released to the scientific community, and applications for funding are accepted. Next, review committees score the applications. Finally, awards are made to those applicants with the highest scores, taking into account programmatic relevance and need.

During FY 2000, NIAID completed a strategic plan, *Planning for the 21st Century*. The document describes broad-based Institute priorities that will guide NIAID programs, policies, and initiatives through the next 3 to 5 years.

NIAID's most recent effort in strategic planning focused on how to further stimulate research activities that address the needs of minority and low-income populations. *The NIAID Strategic Plan for Addressing Health Disparities* specifically identifies goals and objectives that will serve to promote and realize the Plan's vision, which is to eliminate health disparities attributed to infectious and immunologic diseases by 2025.

The full text of the comprehensive Strategic Plan, including descriptions of the opportunities and plans for each goal area, can be accessed at http://www.niaid.nih.gov/strategicplan. The full text of the Health Disparities Strategic Plan can be accessed at http://www.niaid.nih.gov/healthdisparities/niaid_hd_plan_final.pdf.

NIAID Priority-Setting Process



★ - Council meetings

Technology Transfer

Technology transfer in Federal laboratories facilitates the dissemination of new technologies and research materials developed by Government scientists. This technology transfer fuels further innovation and commercialization by the extramural research and development community, ultimately resulting in an improvement in the public health and an increase in the competitiveness of U.S. industry. Federal legislation mandates and defines the Government's technology transfer activities. The key pieces of legislation are the Federal Technology Transfer Act of 1986 and the National Technology Transfer and Advancement Act of 1995.

The NIAID Office of Technology Development (OTD) accomplishes technology transfer by facilitating the transfer of significant research advances and resources to the broader scientific community and the development of collaborative relationships between NIAID scientists, industry, and academia. NIAID uses various mechanisms to accomplish these ends, including Material Transfer Agreements (MTAs), Cooperative Research and Development Agreements (CRADAs), Materials-CRADAs (M-CRADAs), Confidential Disclosure Agreements (CDAs), Clinical Trial Agreements (CTAs), Drug Screening Agreements (DSAs), and through the NIH Office of Technology Transfer (OTT), the patenting of inventions and the negotiation of various license agreements.

NIAID scientists report inventions to OTD by submitting Employee Invention Reports (EIRs). These EIRs are reviewed by OTD and, with the assistance of the NIAID Technology Evaluation Advisory Committee (TEAC), are evaluated for the purpose of filing domestic and foreign patent applications. In FY 2000, TEAC reviewed 25 intramural EIRs and recommended that a patent application be filed on 19 of them. NIAID currently has 329 active patent properties, 100 issued patents, and 229 pending patent applications.

In FY 2000, OTD, together with the three NIAID extramural program divisions—the Division of Acquired Immunodeficiency Syndrome (DAIDS), the Division of Microbiology and Infectious Diseases (DMID), and the Division of Allergy, Immunology and Transplantation (DAIT)—negotiated a total of 46 CTAs, 30 CDAs, and 12 DSAs. NIAID scientists transferred materials under 891 MTAs (including NIAID materials distributed by the AIDS Reference and Reagent Catalog Program). NIAID had a total of 305 active license agreements in FY 2000.

These licenses generated royalty income, which was first used to pay NIAID inventors their share according to Federal law and NIH policy. NIAID also distributed royalty income to intramural laboratories to support research projects and equipment acquisition that otherwise would not have been accomplished with appropriated funds. The remaining royalties were used to pay all of OTD's operating budget, including patent prosecution fees, OTD staff salaries and associated office expenses, as well as overhead charged by OTT.

NIAID scientists performed research under 86 CRADAs and M-CRADAs in FY 2000. A history of NIAID's patent, license, and CRADA activities is provided in the following table.

NIAID Technology Transfer Activities

Fiscal Year	Patents Pending	Patents Issued	Active Licenses	Active CRADAs
1990	57	26	38	11
1992	77	48	69	21
1994	85	65	102	29
1995	96	71	117	31
1996	95	84	156	42
1997	128	91	185	71
1998	154	83	230	95
1999	169	94	278	74
2000	229	100	305	86

Technology Transfer Highlights

Interleukin-2 (IL-2)

The CRADA between NIAID and Chiron Corporation, the provider of IL-2 and the licensee of the patented method of treatment for HIV using IL-2, was extended for 6 years to support two large multisite international phase III studies that began in late 1999. As of February 2001, Chiron has enrolled 931 of the proposed 1,400 patients from 100 sites in eight countries in "A Study of Interleukin-2 (IL-2) in People with Low CD4+ T Cell Counts on Active Anti-HIV Therapy," or "SILCAAT," which evaluates the safety and clinical efficacy of recombinant interleukin-2 (rIL-2; Proleukin®) in patients with advanced HIV infection. As of February 2001, the NIAID-sponsored cooperative group has enrolled 819 of the proposed 4,000 patients from 279 sites in 23 countries in the "Evaluation of Subcutaneous Proleukin® in a Randomized, International Trial," or "ESPRIT," which evaluates Proleukin® safety and efficacy in early HIV infection.

Influenza Virus Vaccine

In 2000, production problems reported by some influenza vaccine manufacturers raised concerns about the possibility of influenza vaccine delays and shortages. NIAID entered into an agreement with Evans Vaccines (formerly Medeva Pharma Limited) because Evans was able to meet its normal annual vaccine production schedule. Under this agreement, negotiated by OTD, Evans made its influenza vaccine (Fluvirin®) available for use in a DMID clinical trial to determine immune responses in healthy adults to half-dose influenza vaccine inoculations. DMID anticipated that a favorable result could effectively extend a limited influenza vaccine supply by doubling the number of doses of the vaccine available to this population. Although an influenza vaccine shortage did not occur in 2000, the data from this trial suggest that administration of half-dose influenza vaccine to healthy adults could have been an acceptable immunization strategy if a public health emergency had developed due to a shortage of vaccine. The half-dose was statistically less immunogenic than the full dose and should not be considered as an alternative under normal circumstances.

Pneumococcal Conjugate Vaccine

Studies have shown that pneumococcus is the most important cause of acute lower respiratory infections, which are the major cause of death and morbidity in Gambian children. The 9-valent investigational pneumococcal conjugate vaccine produced by the Wyeth-Ayerst Research Division, American Home Products, covers about 80 percent of the pneumococcal serotypes prevalent in the upper river division of The

Gambia, and therefore should substantially reduce the incidence of invasive pneumococcal disease in young children and should lower childhood mortality. A clinical trial, funded by NIAID, the U.S. Agency for International Development, the Gates Foundation, and the British Medical Research Council, will recruit and follow approximately 45,000 Gambian children from shortly after birth over a period of $3^1/_2$ years. The Centers for Disease Control and Prevention detailed an epidemiologist to NIAID to work on the trial, and the World Health Organization will serve as a central coordinator. Wyeth-Ayerst will provide its multivalent vaccine for the trial to NIAID under a 5-year CRADA.

Emerging Infectious Diseases

Scientists in the Tuberculosis Research Section of NIAID's Laboratory of Host Defenses, SmithKline Beecham of Pennsylvania (now GlaxoSmithKline), and St. Jude's Children's Research Hospital of Memphis have entered into a research collaboration to produce new medicines for the treatment of emerging infectious diseases, including tuberculosis, methicillin-resistant staphylococcus, and vancomycin-resistant enterococcus. The contributions by GlaxoSmithKline and its subcontractor, St. Jude's, are funded under the new NIAID Challenge Grants program. This collaboration between government and industry uses the expertise of each component to form a drug-development team aimed at neglected diseases with limited or unpredictable markets that might otherwise not be the focus of drug-discovery programs. The Challenge Grants program is designed to facilitate the development of therapeutics for diseases with significant public health impacts but marginal markets by providing dollar-for-dollar matching funds for industrial investment in these R&D areas.

BioTechnology Engagement Program

In a program organized under the auspices of the International Science and Technology Center, the DHHS Office of International and Refugee Health (OIRH) has established the BioTechnology Engagement Program (BTEP) to facilitate the reentry of biological weapons scientists in the Former Soviet Union to areas of science relevant to their domestic health and medical problems. The NIH participates in BTEP through an umbrella agreement with OIRH, managed by NIAID's DMID. Tuberculosis is an important problem throughout Eastern Europe, particularly in Russia, and drug-resistance rates are among the highest anywhere in the world as a result of a collapsed public health infrastructure. Scientists in the Tuberculosis Research Section of NIAID's Laboratory of Host Defenses, scientists at the State Research Center for Applied Microbiology at Obolensk, Russia, and scientists at the Russian Academy of Sciences in Moscow have entered into a BTEP agreement to characterize phenotypic and genotypic aspects of clinical isolates of drug-resistant strains of *Mycobacterium tuberculosis* obtained from throughout the Former Soviet Union. Former weapons scientists from Obolensk will receive training at the Russian Academy of Sciences and in appropriate laboratories in the United States, including the NIH.

Other Office of Technology Development Activities

OTD has begun to provide technology transfer services to the NIAID Dale and Betty Bumpers Vaccine Research Center (VRC), a state-of-the-art biomedical research laboratory on the NIH campus that will facilitate the development of vaccines for HIV and the Ebola virus through the efforts of Dr. Gary J. Nabel, Director, and other members of the VRC staff, in collaboration with researchers at companies and universities.

This year, the NIH adopted the Simple Letter Agreement (SLA), an MTA with simplified terms to reduce the administrative burden and to expedite the process associated with the transfer of materials to and from the NIH.

OTD is working closely with NIAID's DAIT staff and scientists in the Immune Tolerance Network, which involves nearly 40 research institutions internationally, to establish technology transfer agreements. The Network is a major collaborative effort that solicits, develops, implements, and assesses clinical strategies and biological assays for the purposes of inducing, maintaining, and monitoring tolerance in humans for kidney and islet transplantation, autoimmune diseases, and allergy and asthma.

NIAID and the Malaria Vaccine Initiative (MVI) at the Program for Appropriate Technology in Health (PATH) signed a Memorandum of Understanding (MOU) to speed the development of malaria vaccines and to allow for greater collaboration in malaria vaccine research. PATH, a Seattle-based nonprofit organization, established the MVI through a $50 million grant from the Bill and Melinda Gates Foundation to help remove critical barriers to getting a safe and effective malaria vaccine into widespread use.

During FY 2000 NIAID scientists entered into the following four new CRADAs:

- **Merck and Company**—S. Straus, M.D., "A Double-Blind, Placebo-Controlled Study of the Efficacy of Live, Attenuated Oka/Merck Varicella-Zoster Vaccine in Reducing the Incidence and/or Severity of Shingles in Adults"

- **Wyeth-Lederle Vaccines, American Home Products Corporation**—P. McInnes, Ph.D., "Preventing Childhood Mortality—An Efficacy Trial of a Pneumococcal Conjugate Vaccine in Upper and Central River Divisions, The Gambia"

- **American Home Products**—J. Cohen, M.D., "Identification of Varicella-Zoster Gene Targets"

- **Genetics Institute**—T. Wynn, Ph.D., "Development of IL-13 Antagonism as a Treatment for Fibrosis in Schistosomiasis"

CRADAs FY 2000

Investigator	Company	Title
Cliff Barry, Ph.D. Laboratory of Host Defenses	Pharmacopoeia, Inc.	High throughput screening for novel antituberculosis chemotherapies
Cliff Barry, Ph.D. Laboratory of Host Defenses	Sequella, Inc.	High throughput synthesis and screening of novel antitubercular compounds
Jeffrey Cohen, M.D. Laboratory of Clinical Investigation	American Home Products	Identification of varicella-zoster gene targets
Peter Collins, Ph.D. Laboratory of Infectious Diseases	Lederle Praxis	Production of a live, attenuated, respiratory syncytial virus (RSV) and PIV vaccine viruses from cDNA
Pamela McInnes, Ph.D. Division of Microbiology and Infectious Diseases	Aviron	Development of a live, attenuated, cold-adapted influenza vaccine
Pamela McInnes, Ph.D. Division of Microbiology and Infectious Diseases	Wyeth-Lederle Vaccines	Preventing childhood mortality—an efficacy trial of a pneumococcal conjugate vaccine in upper and central river divisions, The Gambia
MaryAnn Guerra, NCI Larry Wolfe, Ph.D., NIAID Office of Technology Information Systems	Applied Research & Technology	Development of an electronic procurement system commodity identification, production and service acquisition, and budget tracking
B. Fenton Hall, M.D., Ph.D. Division of Microbiology and Infectious Diseases	Genzyme Transgenics	Transgenic malaria vaccine: process development; preclinical and initial clinical evaluation
Albert Z. Kapikian, M.D. Laboratory of Infectious Diseases	Wyeth-Lederle	Development of a live, orally administered rhesus rotavirus vaccine
Louis Miller, M.D. Laboratory of Parasitic Diseases	Hong Kong Institute of Biotechnology	An antimalaria, transmission-blocking vaccine—development, scale-up, and manufacturing
David L. Klein, Ph.D. Division of Microbiology and Infectious Diseases	GlaxoSmithKline	A prospective, randomized, double-blind trial to evaluate acellular pertussis vaccine
H. Clifford Lane, M.D. Laboratory of Immunoregulation	Cell Genesys, Inc.	Adoptive transfer of human T-cell clones for treatment of immunologically mediated and infectious diseases
H. Clifford Lane, M.D. Laboratory of Immunoregulation	Chiron	Research and development of IL-2 as a treatment for HIV infection

Catherine Laughlin, Ph.D. Division of Microbiology and Infectious Diseases	Protein Design Labs, Inc.	Production and clinical evaluation of a human anti-herpes simplex virus (HSV) monoclonal antibody as a therapeutic agent for the treatment of neonatal HSV
Harry L. Malech, M.D. Laboratory of Host Defenses	Baxter/Nexell	Development of an *ex vivo* stem cell gene therapy system to provide both short- and long-term correction to the genetic defects in chronic granulomatous disease (CGD)
Louis Miller, M.D. Laboratory of Parasitic Diseases	Hong Kong Institute of Biotechnology	Process development, scale-up, manufacturing, and initial clinical testing of stem cells to provide correction for patients with CGD
Brian R. Murphy, M.D. Laboratory of Infectious Diseases	American Cyanamid	Development of safe and effective live, attenuated vaccines for respiratory syncytial virus subgroups A and B and for parainfluenza viruses type 1, 2, and 3
Robert H. Purcell, M.D. Laboratory of Infectious Diseases	GlaxoSmithKline	Development of a hepatitis A vaccine
Robert H. Purcell, M.D. Laboratory of Infectious Diseases	GlaxoSmithKline	Development of a hepatitis C vaccine
Robert H. Purcell, M.D. Laboratory of Infectious Diseases	GlaxoSmithKline	Development of a hepatitis E vaccine
Alexander Rosenthal Office of Technology Information Systems John McGowan, Ph.D. Division of Extramural Activities	RAMS, Inc.	Development of integrated systems for the receipt, review, award, and tracking of research
Stephen Straus, M.D. Laboratory of Clinical Investigation	Merck and Company	A double-blind, placebo-controlled study of the efficacy of live, attenuated Oka/Merck varicella-zoster vaccine in reducing the incidence and/or severity of shingles in adults
Tom Wynn, Ph.D. Laboratory of Parasitic Development	Genetics Institute	Development of IL-13 antagonism as a treatment for fibrosis in schistosomiasis

Division of Extramural Activities

The Division of Extramural Activities (DEA) (http://www.niaid.nih.gov/dea/) serves NIAID's extramural research community and the Institute in several key areas: overseeing policy and management for grants and contracts; managing NIAID's training program; and conducting initial peer review for funding mechanisms with Institute-specific needs. DEA also provides broad policy guidance to Institute management and oversight of all of NIAID's chartered committees. The Office of the Director, DEA, is a long-time leader of NIH reinvention experiments, including the creation of innovative electronic systems that have changed NIAID and NIH operations.

DEA staff members in every part of the organization interact intensively with grantees, contractors, reviewers, members of the National Advisory Allergy and Infectious Diseases Council (NAAID), and applicants, as well as with the staff of the other NIAID extramural divisions—the Division of Acquired Immunodeficiency Syndrome; the Division of Allergy, Immunology and Transplantation; and the Division of Microbiology and Infectious Diseases.

DEA's Grants Management Branch issues all NIAID grant awards after negotiating the terms of the grant award with the applicant. Specialists in the Branch determine the amount of the award, develop the administrative terms and conditions, and release the official award document. They help clarify grant policies and procedures for investigators and answer their business and administrative questions, such as what costs are allowable and how to formulate a budget for a grant application. Grant specialists supervise day-to-day administrative and financial management of Institute grants and cooperative agreements, while ensuring that NIAID's grants are in compliance with existing policies. They are sources of valuable information on existing and new policies that may alter a grantee's requirements and privileges and that can inform grantees about which actions need approval and from whom.

Contract specialists manage the administrative aspects of NIAID's research and development contract portfolio. Toward those ends, they help develop requests for proposals, negotiate the technical and business aspects of proposals, and select the offeror. Working in DEA's Contract Management Branch (CMB), contract specialists are well versed in a full range of legal, technical, business, and cost-related topics, including Federal Acquisition Regulations and other policies and procedures. They provide investigators with guidance on changes in the scope of the research, the allowability of costs, and other administrative issues, including the use of contract funds, the technical or administrative performance of a contract, current or anticipated initiatives, and changes to a contract. For more information about contracts, go to CMB's World Wide Web site http://www.niaid.nih.gov/contract.

The Scientific Review Program (SRP) conducts peer review of NIAID's contract proposals and grant applications that address Institute-specific needs. These typically include program projects (P), cooperative agreements (U), training (T), and research career (K) grants, as well as applications responding to requests for applications and requests for proposals. Working in DEA's SRP, Institute review staff members assist investigators and NIAID staff with issues related to grant and proposal preparation, including application format and documentation requirements. They can also

provide insights into the peer review process and plans for specific review meetings; give advice on applying for a grant, including special review criteria and other requirements of NIAID program announcements, requests for applications, and requests for proposals; answer questions about the assignment or scheduling of applications or proposals for review; and advise applicants on NIH policy requirements. SRP manages NIAID's three chartered review committees and convenes special emphasis panels as needed.

DEA's Referral and Program Analysis Branch (RPAB) is the Institute's referral point for grant applications. RPAB also performs scientific classification and data analysis of all funded grants, contracts, and intramural research projects, including the categorization and analysis needed to generate official NIAID science-information reports.

Several offices and staff members in DEA's Office of the Director play specialized roles for the extramural community and the Institute. DEA staff members are a focal point for facilitating and coordinating several key activities, including small business programs (Small Business Innovation Research [SBIR] and Small Business Technology Transfer [STTR]), Academic Research Enhancement Award (AREA) grants, Council activities, and extramural communications. They develop policies and processes for NIAID's extramural research programs, including innovative electronic systems, and provide guidance on grant requirements and procedures to investigators.

The Office of Special Populations and Research Training (OSPRT) oversees NIAID's portfolio of training grants, fellowships, and career-development awards. Staff members in this office answer questions that applicants have about training-type support awards supported by NIAID. In addition, OSPRT administers the Research Supplements for the Underrepresented Minorities Program, which supports young minority scientists on NIAID-funded research grants.

The Committee Management Office oversees the legal and policy requirements for NIAID's chartered committees, which include the National Advisory Allergy and Infectious Diseases Council, Board of Scientific Counselors, AIDS Research Advisory Committee, special emphasis panels, and three review committees.

To keep the Institute's extramural research community informed and to provide advice on many research and policy topics, DEA produces the NIAID *Council News* newsletter and sponsors the *Council News* Extramural Information Center on the World Wide Web (http://www.niaid.nih.gov/ncn/). These outreach resources keep grantees, applicants, and staff up to date on Institute funding opportunities, policy changes, and other news. They also educate our extramural constituency by providing budget and payline information, a glossary of NIH terms and acronyms, articles on complex subjects such as percentiling, and advice on writing a grant application.

Division of Acquired Immunodeficiency Syndrome

Mission

The Division of Acquired Immunodeficiency Syndrome (DAIDS) (http://www.niaid.nih.gov/daids/) was formed in 1986 to address the national research needs created by the advent and spread of the HIV/AIDS epidemic. Specifically, the Division's mission is to increase basic knowledge of the pathogenesis, natural history, and transmission of HIV disease and to support research that promotes progress in its detection, treatment, and prevention. DAIDS accomplishes this through planning, implementing, managing, and evaluating programs in (1) fundamental basic research, (2) discovery and development of therapies for HIV infection and its complications, and (3) discovery and development of vaccines and other prevention strategies.

Scientific Areas of Focus

Basic Research

HIV pathogenesis research increases our understanding of the biology of HIV by studying the virus' life cycle, virus-host interactions, and mechanisms of disease progression and transmission. HIV pathogenesis research also supports studies of how the immune system responds to the virus. Knowledge gained from these studies enhances the ability of researchers to create new agents and vaccines to combat HIV infection.

The Division supports a large portfolio of investigator-initiated grants that are pursuing research focused on, but not limited to, the following areas: mechanisms of viral entry and infection, including the role of coreceptors and other cellular accessory molecules; the structure, function, and mechanism of action of viral genes and proteins; development of *in vitro* and *ex vivo* assays to monitor virus growth and immune responses against HIV, and animal models for research on the regulation and function of viral proteins and genetic regulatory sequences; the immunological and virological events controlling primary infection; factors affecting latent reservoirs of HIV; and host factors that modulate viral infection and/or disease progression.

The Division's basic research efforts have yielded significant scientific information about HIV. For example, in recent years, DAIDS-funded investigators have identified new structures for viral components of HIV, additional chemokine coreceptors, and the existence of multiple, persistent HIV reservoirs even with the use of highly active antiretroviral therapy (HAART). Despite these advances, questions still remain about the molecular interactions involved in the regulation of HIV expression and replication. More information also is needed about how the virus evades the immune system to identify additional targets against which therapeutic interventions and vaccines can be directed.

Therapeutics

Therapeutics for treating HIV-1 and its associated opportunistic infections (OIs) are discovered through a number of approaches beginning with basic research on the structure and function of viral and cellular proteins critical to the virus life cycle.

To foster drug development of new HIV therapies, DAIDS supports research on potential new cellular and viral therapeutic targets and new approaches to validate targets; molecules that could effectively block HIV replication; improved formulation of existing agents; approaches to restore the immune

system of HIV-infected individuals; molecular and genetic approaches to protect susceptible, uninfected cells; combination regimens that impede the emergence of viral resistance; and assays to measure restored immunity of HIV-infected individuals.

The evaluation of new drugs and therapeutic agents in people is another critical aspect of therapeutic research. These clinical studies define which new agents are effective against HIV and its associated OIs and also clarify how best to use these drugs.

DAIDS-sponsored therapeutics research has already had a dramatic impact on our understanding of the pathogenesis and clinical management of HIV infection over the last decade. Studies conducted by DAIDS-funded clinical trials research networks have (1) helped to define international guidelines for the treatment of primary HIV infection and associated OIs and prophylactic regimens for these secondary infections; (2) identified biological markers, such as CD4+ counts and viral load for predicting a drug's effectiveness and disease progression; and (3) demonstrated the use of antiretroviral drugs for preventing mother-to-infant transmission. More recent studies have shown that highly active antiretroviral therapy—regimens including reverse transcriptase and potent protease inhibitors—are capable of suppressing HIV viral load to undetectable levels in many infected individuals and partially restoring immune function. Such regimens have had a dramatic impact on HIV mortality in this country.

Nonetheless, treatment failures occur as a result of the development of resistance and/or noncompliance with complicated and often toxic regimens. Moreover, damage to the immune system is incompletely reversed. Thus, there is an ongoing, urgent need for new therapeutic agents and new ways to boost the immunity and rebuild and replace immunity lost to HIV infection. In addition, strategies to address critical questions regarding the long-term effects of antiretroviral therapy and the most optimal approaches to medical management are being developed.

Vaccine and Prevention Research

The discovery and development of an HIV/AIDS vaccine for the prevention of HIV infection and AIDS is a high priority of NIAID.

Through a balanced HIV program that integrates both basic research and empiric testing of candidate vaccines, NIAID supports a broad spectrum of research and development on HIV/AIDS vaccines. Preclinical vaccine research and development examines new vaccine concepts or approaches and new ways to deliver HIV antigens to people and to safely induce a potent anti-HIV immune response. Studies in animal models are aimed at defining how a vaccine could protect the host. For now, clinical evaluations in humans provide the only way of determining whether a vaccine candidate could trigger a safe and effective anti-HIV response in people.

NIAID also supports comprehensive research on other biomedical/behavioral prevention approaches, including drugs and/or vaccines that prevent mother-to-infant HIV transmission, for example, during breastfeeding, microbicides for preventing sexual transmission of HIV, interventions that reduce behaviors that expose people to HIV, programs to reduce intravenous drug abuse, measures to control other sexually transmitted

diseases, and antiretroviral therapies that may reduce the spread of HIV from infected people to their partners. This comprehensive vaccine and prevention program has led to a number of significant scientific advances in vaccine and prevention research. In the past, NIAID-supported researchers have improved the ability of vaccines to induce an antibody response by modifying the envelope protein, elucidated the envelope structure of HIV, advanced our understanding of the role of cellular responses in controlling HIV, developed improved assays for measuring cytotoxic T lymphocytes (CTLs), developed new and better animal models for testing candidate vaccines, and evaluated promising candidates in animal and clinical studies.

To accelerate identification of effective vaccine candidates, future studies will need to address the significance of latently infected resting T cells, study immune responses induced by current vaccine candidates, and assess the impact of HIV and human leukocyte antigen diversity. In addition, the relevance of simian immunodeficiency virus/simian human immunodeficiency virus (SIV/SHIV) models (SIV is an HIV-like virus that infects nonhuman primates; SHIV is a genetically engineered hybrid virus that has an HIV envelope and an SIV core) and the utility of novel vaccine designs must be explored. With regard to prevention research, new microbicides need to be developed and tested, and new regimens for preventing maternal-infant transmission during breastfeeding, which are effective and practical for developing countries, need to be explored. Lastly, because the majority of new infections are occurring in the developing world, NIAID's vaccine and prevention research activities are conducted on a global scale.

These research programs are designed to define global research priorities, ensure the clinical relevance of future vaccine and prevention strategies to human populations most in need, strengthen collaborations with local investigators worldwide, and support training and infrastructure development in developing countries.

The coordination of this complex program of AIDS research is an important function of DAIDS. By surveying developments in key scientific areas, DAIDS assesses ongoing needs in biomedical research as well as requirements for outreach activities and for training scientific investigators. As part of this process, DAIDS works with advisory groups and community and health professional organizations in evaluating and redirecting program emphases to respond to changing research needs.

Major Programs

- Acute Infection and Early Disease Research Network
- Adult AIDS Clinical Trials Group
- AIDS Research and Reference Reagent Program
- Centers for AIDS Research
- HIV Prevention Trials Network
- HIV Therapeutics: Targeting Research Gaps
- HIV Vaccine Design and Development Teams
- HIV Vaccine Research and Design Program

- HIV Vaccine Developmental Resources Contracts
- HIV Vaccine Trials Network
- Innovation Grant Program
- Integrated Preclinical/Clinical Vaccine Development Program
- Laboratory Methods to Assess Responses to HIV Vaccine Candidates
- Mechanisms of AIDS Pathogenesis Collaborative Teams
- Mucosal Immunity in Pathogenesis/ Prevention of Human Disease Program
- Multicenter AIDS Cohort Study
- National Cooperative Drug Discovery Groups—OI
- Novel HIV Therapies: Integrated Preclinical/Clinical Program
- Pediatric AIDS Clinical Trials Group
- Simian Vaccine Evaluation Units
- Terry Beirn Community Programs for Clinical Research on AIDS
- Women and Infants Transmission Study
- Women's Interagency HIV Study

Division of Allergy, Immunology and Transplantation

The Division of Allergy, Immunology and Transplantation (DAIT) (http://www.niaid.nih.gov/dait/) supports research that focuses on understanding the important role of the immune system in the pathogenesis, treatment, and prevention of many immune-mediated diseases, including asthma and allergic diseases; autoimmune disorders, such as type 1 diabetes, rheumatoid arthritis, and systemic lupus erythematosus; inherited primary immunodeficiency diseases; and the transplantation of solid organs, tissues, and cells. Collectively, these chronic diseases affect tens of millions of Americans, resulting in considerable morbidity, mortality, pain and suffering, and high medical costs. Immune-mediated diseases cross many clinical specialties, and knowledge of the immune system and its role in disease is increasingly important in the clinical management of patients with these disorders.

DAIT supports basic, preclinical, and clinical research to enhance our understanding of the causes and mechanisms that lead to the development of immune-mediated diseases and to generate an expanded knowledge base that can be applied to the development of improved means of diagnosis, prevention, and treatment. Through outreach, demonstration, and education projects, DAIT supports testing the effectiveness of interventions to promote health and prevent disease in defined populations. DAIT's approach integrates the disciplines of basic science with relevant clinical specialties. The Division pursues its research goals by fostering research initiated by individual investigators; by supporting multidisciplinary program projects that explore the mechanisms of immune-mediated diseases, transplantation immunology, and the basic biology of the immune system; and by sponsoring clinical research programs to assess the safety and efficacy of new therapeutic approaches. Support also is provided for interdisciplinary cooperative research centers on asthma and other allergic, autoimmune, and immune-mediated diseases.

DAIT's research programs are placing increasing emphasis on the preclinical and clinical development of new tolerogenic and immunomodulatory approaches for the prevention and treatment of transplant rejection and for the treatment of asthma and other allergic and autoimmune diseases. Another area of rapid program growth focuses on the application of emerging technologies to advance fundamental understanding of immunologic principles and to develop diagnostic and prognostic tools, and surrogate markers of disease activity and therapeutic effect.

The Division's basic immunology investigations focus on the properties, interactions, and functions of immune system cells and the substances produced by those cells. Information generated through such fundamental research provides the knowledge base necessary to develop prevention and treatment strategies. To promote research on these fundamental aspects of immune system functioning, DAIT supports multidisciplinary Program Projects on the Biology of the Immune System, Mechanisms of Peripheral Immunologic Tolerance and Anergy, Basic Biology of the Immune Responses for Vaccine Research, Transplantation Immunology, and Autoimmunity. Clinical immunology studies focus on a broad spectrum of diseases, including those that affect the intestines, joints, nervous system, and endocrine system. Research in these clinical areas is supported by Program Projects on Mucosal Immunity, Autoimmune Disease, and Methods of

Immune Intervention. In addition, support is provided for research to enhance understanding of the causes and mechanisms of various inherited immunodeficiency diseases, such as severe combined immunodeficiency disease (SCID).

NIAID has made immune tolerance a major priority and, as part of its scientific planning process, developed a broad-based, long-range plan to accelerate research in this important area. As a result of this planning process, DAIT established the Immune Tolerance Network (ITN) in FY 1999. The ITN, cosponsored by the National Institute of Diabetes and Digestive and Kidney Diseases and the Juvenile Diabetes Research Foundation International, is designed to conduct clinical trials of promising tolerogenic approaches, carry out integrated studies of underlying mechanisms, and develop surrogate/biomarkers of the induction and loss of tolerance in humans. This international multi-institutional research program is focused on four clinical areas: kidney transplantation, islet transplantation, autoimmune diseases, and asthma and allergic diseases.

Allergic diseases, including asthma, are among the major causes of illness and disability in the United States. Studies to examine the causes, pathogenesis, diagnosis, treatment, and prevention of allergic diseases represent a major focus of DAIT's basic and clinical research portfolio. Through the Inner-City Asthma Study, DAIT supports a multicenter clinical intervention to reduce asthma severity among inner-city children. DAIT's national network of Asthma and Allergic Diseases Research Centers focuses primarily on the underlying immune mechanisms involved in these disorders and on approaches to improve diagnosis and treatment.

Autoimmune diseases, such as type 1 diabetes and rheumatoid arthritis, afflict 5 percent of the U.S. population and are a major cause of chronic disability, particularly among women. DAIT-supported programs in this area promote the integration of basic and clinical research as well as interdisciplinary and trans-NIH collaborations. Program projects and individual research projects elucidate mechanisms of the etiology and pathology of autoimmunity and autoimmune diseases, including basic molecular and cellular studies, genetic studies, the development of new therapeutics, and preclinical and clinical research.

DAIT's basic research in transplantation immunology and genetics seeks to delineate the organization and effects of gene expression on immune function and to determine the manner in which the products of gene expression control the immune response to foreign substances, such as transplanted organs and cells. In addition, DAIT supports individual research projects focused on the regulation of the immune response and Program Projects in Transplantation Immunology. DAIT also supports clinical research to evaluate new therapeutic approaches to improve the engraftment and survival of transplanted organs through the Cooperative Clinical Trial in Adult Kidney Transplantation and the Cooperative Clinical Trial in Pediatric Kidney Transplantation.

Programs

Asthma and Allergic Diseases

- Asthma and Allergic Diseases Research Centers
- Inner-City Asthma Study (ICAS)
- Program Projects on Allergic and Respiratory Diseases

Autoimmune Diseases
- Autoimmunity Centers of Excellence
- New Imaging Technologies for Autoimmune Diseases
- Multiple Autoimmune Disease Genetics Consortium
- North American Rheumatoid Arthritis Consortium
- Clinical Trials in Stem Cell Transplantation for the Treatment of Autoimmune Diseases
- Immunologic Phenotyping of Mouse Mutants
- Clinical Trials in Immunologic Diseases
- Clinical Markers of Immune-Mediated Diseases
- Diabetes Centers of Excellence
- Diabetes Prevention Trial—Type 1
- Cooperative Study Group for Autoimmune Disease Prevention

Basic and Clinical Immunology
- Human Immunology Centers of Excellence
- Hyperaccelerated Award/Mechanisms in Immune Disease Trials
- Program Projects on Basic Biology of the Immune Responses for Vaccine Research
- Program Projects on Basic Parameters of Human Immunology
- Program Projects on the Biology of the Immune System
- Program Projects on Mechanisms of Peripheral Immunologic Tolerance and Anergy
- Program Projects on Mucosal Immunity
- Application of Data on the HLA System to the Development and Improvement of Vaccines
- Repository of Transgenic and Gene-Targeted Mutant Mice
- NIAID Tetramer Facility

Immune Tolerance
- Immune Tolerance Network
- Non-Human Primate Transplant Tolerance Cooperative Study Group

Mucosal Immunity
- Program Projects in Mucosal Immunity
- Innovative Research in Human Mucosal Immunity
- Mucosal Immunity in Pathogenesis/ Prevention of Human Disease

Primary Immunodeficiency Disease
- Program Projects on Human Immunodeficiencies
- Primary Immunodeficiency Disease Registry
- Clinical Trials in Primary Immunodeficiency Diseases

Transplantation
- Cooperative Clinical Trials in Adult Kidney Transplantation
- Cooperative Clinical Trials in Pediatric Kidney Transplantation
- International Histocompatibility Working Group
- NIAID-Juvenile Diabetes Research Foundation International Program Projects in Transplantation Tolerance
- Program Projects in Transplantation Immunology
- Program Projects in Mechanisms of Chronic Rejection

Division of Microbiology and Infectious Diseases

The Division of Microbiology and Infectious Diseases (DMID) (http://www.niaid.nih.gov/dmid/) supports extramural research to control and prevent diseases caused by virtually all human infectious agents except HIV. DMID supports a wide variety of projects spanning the spectrum from basic biomedical research, such as studies of microbial physiology and antigenic structure, through applied research, including the development of diagnostic tests, experimental drugs, and vaccines, to the conduct of clinical trials to test the safety and efficacy of new disease-prevention strategies. NIAID also funds projects to sequence the full genomes of a number of medically important microbes, which can be exploited in many ways, for example, to trace microbial evolution, to discover targets for vaccine and drug development, and to identify mutations that contribute to drug resistance.

Research areas in basic bacteriology and mycology include molecular structure and function, genetics, biochemical composition, and physiological and biochemical processes. Studies on these pathogens extend basic insights to identify antigens that might serve as vaccine candidates and features that might be targeted by drugs and to examine mechanisms of infection, pathogenicity, and virulence. Areas of particular interest include streptococci, pneumonia, nosocomial infections, fungal infections, antibiotic resistance, bacterial infections, sexually transmitted diseases (STDs), and bacterial diarrheas.

Research areas in virology include molecular structure and function, genetics, synthesis, and reproduction of viruses; characterization of viral proteins and nucleic acids; mechanisms of pathogenicity, latency, persistence, and reactivation; interactions with immune systems; and vaccine development. Basic information is being used to combat important viral diseases such as influenza, herpes, congenital cytomegalovirus infection, hepatitis, human papillomavirus (HPV) infection, and viral diarrheas.

Research on parasites involves the application of biochemical, genetic, and immunologic approaches. Studies of parasites are leading to the identification of protective and diagnostic antigens and to the development of more effective drugs. In addition, studies of insect vectors are aimed at controlling the transmission of important pathogens such as malaria. Because parasitic and other tropical diseases are international health problems, the Division also supports clinical studies in regions where these infections are endemic through the Tropical Medicine Research Centers and International Collaboration in Infectious Disease Research programs.

An area of particular focus is emerging infectious diseases. The threat posed by disease-causing microbes is expected to continue and perhaps even intensify in coming years. New infectious disease problems have continued to emerge recently, whether they are old diseases that have undergone dramatic increases, the new association of chronic diseases as sequelae of acute illnesses, opportunistic infections, viral infections most recently associated with cancers, or new diseases that are now impinging on the public consciousness. DMID, by supporting a broad spectrum of research in infectious diseases, has the capacity to focus the research agenda to better understand the epidemiology, pathogenesis, and microbiology of emerging

infections and infectious diseases and, ultimately, to develop mechanisms to control and prevent them. Examples include the emergence of new infectious agents, such as West Nile virus, hepatitis C, and *Helicobacter pylori*, and the reemergence of old diseases, such as influenza and tuberculosis (TB). In FY 2000, DMID funded a number of grants on emerging diseases through its Challenge Grants Program, a new initiative that provides matching funds to companies that will commit their own dollars and resources toward developing new drugs and vaccines against malaria, TB, influenza, and dengue virus.

Toward preventing disease, one of the primary goals of the Division is to develop new and improved vaccines and strategies for vaccine delivery for the entire spectrum of infectious agents—bacteria, viruses, fungi, and parasites. An integral component of these efforts is the evaluation of vaccine safety, which is assessed in every vaccine clinical trial sponsored by NIAID.

DMID also supports numerous efforts aimed at developing more effective diagnostic tools for infectious diseases. Examples include diagnostic tests for STDs and Lyme disease, and the development of antimicrobial resistance markers.

Internationally, DMID/NIAID participates with other national research agencies in the development and support of programs such as the Global Alliance for Vaccines and Immunization (GAVI) and the Multilateral Initiative on Malaria (MIM). GAVI was established in 1999 as an alliance of global partners to replace the Children's Vaccine Initiative. The mission of GAVI is to save children's lives and protect people's health through the widespread use of safe vaccines.

Finally, DMID maintains a drug-development program that supports research at three levels: drug discovery (accomplished by screening and by targeted molecular research), preclinical evaluation (in animal models of human infections), and clinical trials (evaluation of new therapies in humans).

Primary Research Areas

Antimicrobial Resistance
- Network on Antimicrobial Resistance in *Staphylococcus aureus*
- Interagency Task Force on Antimicrobial Resistance
- Bacteriology and Mycology Study Group (BAMSG)

Antiviral Research
- Collaborative Antiviral Study Group
- Collaborative Antiviral Testing Group
- Antiviral Drug Discovery

Chronic Fatigue Syndrome (CFS)
- CFS Cooperative Research Centers (CRCs)

Emerging Diseases (also captured by specific disease areas)
- West Nile Virus, Hantavirus, Dengue, and Other Emerging Threats
- Ecology of Infectious Diseases
- International Training and Research on Emerging Infectious Diseases

Fungal Diseases
- Mycology Research Units (MRUs)
- BAMSG

Genomics
- Support 35 Active Sequencing Projects (http://www.niaid.nih.gov/cgi-shl/genome/genome.cfm)
- Microbe Project Interagency Working Group

Hepatic and Enteric Diseases
- Hepatitis Animal Models
- Hepatitis C Virus Cooperative Research Centers (HCV CRCs)
- Enteric Pathogens Research Unit (EPRU)

International Centers for Tropical Disease Research
- International Collaboration in Infectious Disease Research (ICIDR)
- Tropical Disease Research Units (TDRUs)
- Tropical Medicine Research Centers (TMRCs)

Lyme Disease
- Development of Diagnostic Approaches and Vaccine Candidates
- Animal Models
- Clinical Studies

Malaria
- Malaria Vaccine Design and Development
- *Plasmodium falciparum* Genomic Sequencing Project
- Clinical Research and Trial Preparation Sites in Endemic Areas
- Malaria Research and Reference Reagent Resource

Respiratory Diseases
- Respiratory Pathogens Research Unit
- Maternal Immunization
- Acellular Pertussis Vaccine Trials
- Influenza Vaccine Development
- Interagency Pandemic Planning Group on Influenza

Sexually Transmitted Diseases (STDs)
- Animal Models for STDs
- Research on Molecular Immunology of STDs (ROMIS)
- STD Clinical Trials Unit (CTU)
- STD Clinical Research Centers
- STD Diagnostic Development
- Topical Microbicides Program

Tuberculosis (TB)
- Animal Models for TB
- TB Diagnostic Development
- TB Research Materials
- TB Research Unit
- TB Vaccine Development

Vaccine Research and Development (also captured by specific disease areas)
- Vaccine and Treatment Evaluation Units
- Vaccine Production Facility
- Regulatory and Biostatistical Support Groups
- Immunization Safety Review Committee

Division of Intramural Research

The Division of Intramural Research (DIR) (http://www.niaid.nih.gov/dir/) is home to NIAID's renowned laboratories and clinical research programs, which cover a wide range of biomedical disciplines related to immunology, allergy, and infectious diseases. DIR scientists conduct basic laboratory research in the areas of virology, microbiology, biochemistry, parasitology, epidemiology, mycology, molecular biology, immunology, immunopathology, and immunogenetics.

DIR also conducts over 100 clinical protocols at any given time, using the facilities of the Warren G. Magnuson Clinical Center on the NIH campus. Clinical Center physician-scientists treat patients with a variety of diseases, including AIDS, vasculitis, immunodeficiencies, host defense defects, unusual fungal infections, asthma, allergies, various parasitic diseases, and disorders of inflammation. Frequently, patients participate in studies of new and promising treatments or diagnostic procedures derived from ongoing laboratory research efforts.

In addition to conducting innovative scientific studies, DIR researchers devote considerable effort to mentoring young scientists, teaching, and other academic pursuits. Each year, DIR laboratories host hundreds of predoctoral and postdoctoral trainees who are immersed in the superb scientific setting at the NIH while they participate in DIR's basic and clinical research programs.

The Division and its staff of scientists and physicians have received national and international recognition for their outstanding research achievements. Eight members of the current staff have been elected to the National Academy of Sciences, and many staff members have earned prestigious awards for their contributions to science.

Scientific Resources

Each of the 15 DIR laboratories (http://www.niaid.nih.gov/dir/labs.htm) contains state-of-the-art equipment that is augmented by the expertise and services provided by four supporting branches. DIR scientists share access to sophisticated instruments and techniques such as peptide synthesis, sequence analysis of proteins, mass spectroscopy, confocal microscopy, and 4-channel flow cytometry. DIR has facilities for breeding transgenic and gene-targeted (knockout) mice and provides other animal care services, including extensive in-house animal breeding and holding facilities, oversight of animal protocols, and support to scientists conducting animal studies. Animal care facilities are maintained in Bethesda, Maryland, and at the DIR labs in Hamilton, Montana. Biosafety-level-three facilities for both laboratory and animal studies are available at those locations, as well.

Computer linkages for DIR scientists consist of a local area network within NIAID and a wide area network linking DIR scientists to other areas of the NIH, such as the computer facilities of the NIH Division of Computer Research and Technology. The computer network also provides quick access to the libraries of the NIH Clinical Center and to the National Library of Medicine, and links DIR researchers in the Maryland locations of Bethesda, Rockville, the Frederick Cancer Research and Development Center, and the Rocky Mountain Laboratories in Hamilton, Montana. Teleconferencing equipment further enhances communications between DIR staff and their colleagues across the campus and around the world. In addition, DIR investigators communicate with colleagues at the Malaria Research and Training Center in Mali via direct satellite uplinks, which are

much faster and more dependable than the local Internet service-provider connections.

Immunology Research

In studying immunologic diseases, DIR scientists study both the normal processes of the immune system and how these processes malfunction in the disease state. Much of the research focuses on the B and T lymphocytes, which react to foreign organisms that have entered the body. Findings from the studies are used in several ways. First, they are used in the development of new or improved vaccines that stimulate the immune system to recognize and destroy invading organisms. Second, they help us understand and develop effective treatments for immunodeficiency diseases in which the lymphocytes are lacking or performing inadequately. Finally, they can be used in the elucidation and treatment of autoimmune diseases in which the immune cells attack the body's own cells. Current projects include the following:

- Role of cytokines in the pathogenesis and treatment of autoimmune diseases,
- Immunoregulatory defects in inflammatory bowel disease, and
- Gene therapy for immunodeficiencies.

Allergy Research

Researchers studying allergic diseases concentrate on asthma, allergic reactions involving the skin, nasal passages and sinuses, and chronic food allergy. Much of this research focuses on the mast cell, which plays an important role in many allergic disorders and secretes chemicals such as histamine. Histamine is, in part, responsible for triggering the events that cause the visible signs of an allergic reaction, such as hives, difficulty breathing, or a runny nose. Intramural scientists study how mast cells develop, their gene regulation, and their interactions with other cells in the connective tissue. Other projects are concerned with mucous membrane functions in the respiratory tract, both in normal and allergic individuals, and the role of the autonomic nervous system in causing allergic symptoms. DIR studies include the following:

- Noninvasive imaging of inflammation in asthma,
- Tolerance studies for asthma, and
- Efficacy of a soluble IL-4 receptor in treating asthma.

Infectious Disease Research

DIR programs to improve the treatment and control of infectious diseases involve a multidisciplinary approach aimed at increasing our understanding of pathogenic organisms, the host response to infection, vector biology, and chemotherapeutics. Studies of the organisms—the bacteria, viruses, fungi, and parasites that cause diseases as varied as tuberculosis, AIDS, Lyme disease, and malaria—may reveal opportunities to use drugs to interfere with vital processes within the organism that are necessary for reproduction. Host studies may define the necessary immune response to successfully fight infection and help investigators design effective vaccines, whereas vector studies reveal new targets for public health interventions. DIR investigators are also studying potential infectious etiologies of chronic diseases. Several infectious agents,

such as hepatitis C virus, human papillomavirus, and *Chlamydia pneumoniae*, recently have been associated with chronic illnesses. Examples of ongoing projects in DIR include the following:

- Structured therapy interruption as an AIDS treatment strategy,
- Evaluation of patients with chronic Lyme disease, and
- Malaria studies in Africa.

Vaccine Research

DIR researchers are developing several new and novel vaccines, such as those that might be able to immunize people against more than one disease at the same time. Another example of a novel vaccine is the transmission-blocking vaccine for malaria, which would prevent mosquitoes that had just bitten a malaria-infected person from transmitting the malaria parasite to other individuals. Studies are under way to develop vaccines against pathogenic flaviviruses, especially the dengue virus, which may lead to the development of vaccine candidates for the newly emergent West Nile virus. Investigations continue toward the development of a vaccine against the respiratory syncytial virus, the principal cause of respiratory disease in infants in the United States and the world. In addition, the parainfluenza viruses, which cause respiratory disease in children and adults, are targets for vaccine development in DIR.

Division of Intramural Research Laboratory Review Process

Step 1 Scheduling and Approval	Step 2 Team Selection	Step 3 Preparation for Site Visit	Step 4 Site Visit	Step 5 Site Visit Report and Recommendations	Step 6 Implementation and Recommendations	Step 7 Followup Report
Division of Intramural Research (DIR) Director, DIR, approves date of scheduled review.	Director, DIR, in consultation with Director, NIAID, recommends slate of term appointment and ad hoc candidates for Review Team membership.	DIR laboratory(ies) prepares and forwards research and administrative summaries to Director, DIR, for review. Director, DIR, prepares Review Team interview schedule and forwards materials to Review Team.	Research presentations are made by laboratory staff, and Review Team conducts interviews of selected staff.	Laboratory Chief attends site visit report presentation and has opportunity to comment on draft report of his or her laboratory.	Director, DIR, and Deputy Director, DIR, meet with laboratory staff to discuss report and BSC recommendations. On the basis of the action plan developed by the Director, DIR, laboratory implements the appropriate recommendations provided by Review Team.	BSC recommendations and Director, DIR, response are sent to Deputy Director for Intramural Research, NIH, who obtains further review by selected Scientific Directors of other ICDs. Director, DIR, reports about BSC at next meeting and to the National Advisory Allergy and Infectious Diseases Council.
Board of Scientific Counselors (BSC)	Chairperson, BSC, selects Review Team members.	BSC and Review Team members review materials prepared by DIR laboratory(ies).	Review Team hears presentations and conducts interviews of laboratory staff. BSC develops a preliminary report on site.	BSC preliminary report is presented to Director, DIR, Director, NIAID, and Deputy Director for Intramural Research, NIH, at the Executive Review Session. Final, comprehensive report is typed, edited, and forwarded to Director, DIR, for review and action.		

NIAID Dale and Betty Bumpers Vaccine Research Center

The NIAID Dale and Betty Bumpers Vaccine Research Center (VRC) is dedicated to translating the latest concepts in disease pathogenesis and immunology into new vaccine strategies, providing safe and effective means to prevent and control human diseases. The mission and primary focus of the VRC is to conduct research to develop an effective AIDS vaccine. The global epidemic of HIV infection is one of the most significant infectious disease threats to human health. Although new AIDS diagnoses and deaths have fallen significantly in many developed countries, the HIV/AIDS epidemic continues to accelerate in the developing world. There are an estimated 5.3 million new HIV infections each year, and in 2000, HIV/AIDS was the fourth overall leading cause of mortality worldwide, resulting in an estimated 3 million deaths. Beyond the human tragedy of HIV/AIDS, the epidemic poses a significant impediment to the economic growth and political stability of many countries. In developing countries and in segments of the U.S. population, anti-HIV therapies are frequently beyond financial reach. Accordingly, effective, low-cost tools for HIV prevention are urgently needed to bring the HIV epidemic under control. A globally effective, accessible vaccine remains the best hope for ending this pandemic.[1]

To combat HIV, we now have at our disposal new information about the molecular and immunological basis of disease and improved tools for analysis of virus structure and measurement of immune responses. This scientific knowledge forms the basis for new ideas that may lead to novel strategies for effective vaccination. In addition, the scientific and industrial infrastructure has advanced to facilitate production and evaluation of vaccines. Nonetheless, the process of moving vaccine concepts through preclinical development and into initial clinical trials can be slow and unpredictable. Years of investment and research are required to progress through initial vaccine research, preclinical testing, and development to achieve an effective vaccine. In this setting, the VRC has a unique opportunity and responsibility to facilitate the transition of new concepts in microbial pathogenesis, mechanisms of immunity, and vaccine design into clinical applications.

The impact and importance of vaccines cannot be overstated. Vaccines are powerful public health tools that provide safe, cost-effective, and efficient means of preventing morbidity and mortality from infectious diseases. They have revolutionized the control of infectious diseases, virtually eliminating polio, smallpox, and measles; however, an effective vaccine against HIV poses unique obstacles. HIV strains worldwide display tremendous genetic diversity that may limit the breadth of protective immunity elicited by a single vaccine. Two types of HIV can be distinguished genetically and antigenetically: these have been termed HIV-1 and HIV-2. HIV-2 is endemic in West Africa but is rare outside this region, whereas HIV-1 is the cause of the global pandemic. HIV-1 is subclassified into distinct genetic subtypes, or clades. For reasons that are not clear, these subtypes have distinct geographic distributions. To be effective, an HIV vaccine, or vaccines, will have to elicit immune responses against diverse strains of HIV-1. Also, because HIV attacks the primary cells of the immune system, persistent infection fails to produce

[1] UNAIDS/WHO, AIDS Epidemic Update: December 2000; WHO ISBN: 92-9173-0008-4.

effective immunity in a large percentage of the population. We are just beginning to understand how the virus evades immunologic surveillance to cause persistent infection and disease.

Scientific Areas of Focus

A new science of vaccinology is now emerging that takes advantage of the latest technologies and scientific knowledge to design effective vaccine strategies. This process of rational vaccine design is closely coordinated with evaluation of vaccine candidates in animal models and human clinical trials. By embracing new discoveries and using them for the rational design of experimental vaccines, an iterative process of vaccine development, in which clinical evaluation informs basic research, will be established. The science of vaccinology is by its nature interdisciplinary, combining basic and applied research in immunology, virology, disease pathogenesis, molecular biology, and structural biology with clinical trials methodology. By encompassing these activities at a single center possessing the capacity for vaccine production, the VRC hopes to advance the science of vaccine development.

Basic Research

The VRC aims to develop vaccine candidates that will induce effective humoral and cellular immune responses. Recent data from several animal model systems strongly suggest that both humoral and cellular immunity play key roles in protection against HIV infection and disease. Based on the hypothesis that a combination of potent CD4- and CD8-mediated immune responses, and functional antibodies to appropriate viral epitopes, will prevent HIV infection or control HIV disease, the preclinical research program will explore basic science questions relevant to vaccine design. Guided by continuing research that reveals a better understanding of the basic elements of protective immunity, scientists at the VRC will apply this knowledge toward the design of vaccines. A program in virus structural biology will explore the rational design of immunogens that can induce potent virus-neutralizing antibodies. Development of candidate vaccines will focus on using portions of engineered HIV genes to express specific HIV antigens that will trigger a protective immune response. These genes can be delivered in DNA plasmids (extrachromosomal rings of DNA) and in viral vectors such as poxviruses (including modified vaccinia virus Ankara [MVA] and recombinant canarypox virus) or adenoviruses. In DNA immunization, the host is immunized by direct administration of viral genes. Viral vectors can also be constructed containing one or more HIV genes that will cause infected cells to produce HIV-specific protein in native form. Rodent and primate models will be used in a systematic manner to evaluate safety, immunogenicity (induction of immune response), and degree of protection provided by these candidate vaccines. Such preclinical animal testing will be closely integrated with the basic science programs to provide information for iterative improvements in the development of new immunogens.

A second major goal of the VRC basic research program is the evaluation and optimization of the immune response generated by candidate vaccines. The development of immunogens that elicit protective immunity against HIV will be guided by studies that systematically evaluate the humoral and cellular immune

responses generated by vaccine candidates. Reproducible, validated assays to measure T-cell function and virus particle reduction will be developed and applied to animal studies and human clinical trials. In this way, scientists can determine how effectively the candidate vaccine protects against infection or disease. Preclinical studies in small animals and primates will evaluate vaccine dose, formulation, and delivery route, and will address the immunogenicity of multigene vectors, and vaccine combinations that prime with one immunogen and boost with a second. The accumulated knowledge from these preclinical studies will be used to develop vaccination strategies that induce optimal immune responses. Preclinical animal testing will be closely integrated with VRC basic science and clinical programs to provide information on the advancement of promising candidate vaccines into human trials.

Human Clinical Trials

A systematic, well-coordinated process of human vaccine trials is essential to effectively develop new vaccines. While animal models are invaluable for guiding the development of vaccine approaches in general, and are indispensable for evaluating efficacy and immune correlates of protection, parallel phase I/II studies in humans are required to validate safety and immunogenicity findings. Only human phase III efficacy trials can determine vaccine efficacy. To efficiently move vaccine development forward, the VRC will combine traditional empirical vaccine development with hypothesis-driven basic and preclinical research. This approach will promote an iterative process in which data from clinical evaluation will inform basic research and vaccine design, and findings in animal models will help prioritize approaches to test in clinical trials. In addition to traditional phase I studies in HIV seronegative volunteers, the VRC will study the ability of vaccine candidates to augment native immunity in HIV-infected patients. Intensive evaluation of CD4 and CD8 immune responses will be correlated with control of viral replication and disease progression. In addition to the potential benefit to patients, studies of vaccine therapy will elucidate mechanisms of cellular immunity and T-cell memory that play a role in protection against HIV. Such data can then be applied to the development of preventive vaccines.

The VRC will actively collaborate with intramural and extramural scientists, and facilitate the movement of ideas from the broader community into clinical trials. The VRC will maintain close ties with extramural investigators in the HIV Vaccine Trials Network (HVTN), where the infrastructure for conducting larger scale trials is already established, to characterize safety and comparative immunogenicity of promising vaccine approaches. This collaboration will include efforts to develop vaccine candidates that can be evaluated at international field sites. When products emerge with real promise for licensure, the VRC will also interact with the pharmaceutical industry, in which there is a large capacity for, and experience in, product development and distribution. Therefore, the VRC will fill the gap between new basic concepts in immunology and initiation of clinical trials by applying state-of-the-art methods to rational vaccine design and evaluation at a single site.

Global Health

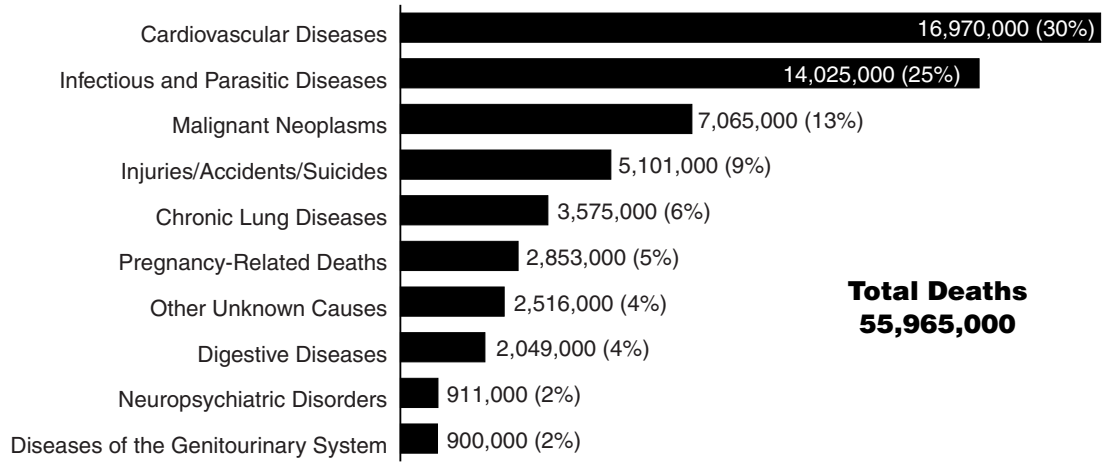
The NIAID research mission in infectious and allergic diseases is of global importance because together these diseases are the most common preventable causes of human illness and death around the world. Recent concern about emerging and reemerging infectious diseases, biological warfare, and the importance of research to improve early diagnosis, prevention, and control has added new dimensions to NIAID international research on these pathogens. Formal recognition of the importance of international research dates back to the International Health Act (1960), which gave the Secretary of Health and Human Services the authority to conduct research activities outside the United States, provided that the activities were beneficial to the health of U.S. citizens. This authority has been delegated to the NIH and to NIAID. The Public Health Service Act of 1988 (P.L. 100-607) created new HIV/AIDS authorities for the NIH. Subsequently, the NIH Revitalization Act (1993) gave NIAID specific authority to conduct research on tropical diseases. These diseases disproportionately affect populations in these parts of the world. As a domestic agency, NIAID uses the following five approaches to carry out international studies.

Intramural Collaborative Research and Research Training

NIAID laboratories become involved in international research projects when these activities are essential to their research efforts. Funding for such collaborations ordinarily comes from each laboratory's regular budget and, for that reason, is usually focused, well defined, and not a major source of financial support. Exceptions may occur when several partners launch a cooperative effort or when the intramural laboratory secures external funding. Examples include the following:

- **Bamako, Mali.** Since 1989, NIAID's Laboratory of Parasitic Diseases (LPD) has been working with scientists and physicians at the National School of Medicine of Mali, located in Bamako, to develop the Malaria Research and Training Center (MRTC). The Center, now a reality, is a well-equipped, highly productive program in which the research is planned, directed, and

Leading Causes of Death Worldwide



WHO: World Health Report, March 2000

executed by Malian staff. Programs at the Center are funded by a number of international and U.S. agencies. Several U.S. and European universities and research organizations have active research collaborations with the MRTC.

In collaboration with the NIH National Center on Minority Health and Health Disparities, the Fogarty International Center, and the University of Maryland School of Medicine, the LPD International Research Unit has developed a training program for young scientists, medical students, and physicians that permits them to gain experience in an African laboratory or medical school. The program has as its primary goal the attraction of under-represented segments of the U.S. population to careers in tropical medicine, but the program is open to applicants from all backgrounds. (For additional detail on the recent dedication of the new malaria laboratory facility, see the Malaria text box, page 54.)

- **Kinshasa, Republic of the Congo.** NIAID's Laboratory of Immunoregulation participated in Project SIDA, the French acronym for AIDS, in the Republic of the Congo (formerly Zaire). Project SIDA was a cooperative effort with the U.S. Centers for Disease Control and Prevention (CDC), the Institute of Tropical Medicine in Antwerp, Belgium, the U.S. Armed Forces Institute of Pathology (AFIP), and the Ministry of Health to study AIDS in the Kinshasa metropolitan area.

Although intramural involvement in international projects is important, the most significant intramural international health activity is the research training of predominantly young foreign scientists in the Visiting Scientists Program. Approximately one-third of scientists in NIAID laboratories are from outside the United States. Individual NIAID laboratories invite outstanding individuals to join them at a formative stage in their postdoctoral careers for research training, which ranges from one to several years. Established foreign scientists may also be invited to join a laboratory for collaborative research. The host NIAID laboratory ordinarily supports stipends for these visiting scientists. In FY 2000, the largest numbers of NIAID visiting scientists were from China, Italy, France, Japan, India, Russia, Australia, Germany, Canada, Korea, and Brazil.

Foreign Awards

NIAID and the NIH accept investigator-initiated research proposals from foreign scientists. To be funded, foreign applications must receive a competitive score by peer review and must be approved for funding by the National Advisory Allergy and Infectious Diseases Council on the basis of their uniqueness and/or program relevance. Foreign investigators may also be eligible to compete for NIAID research contracts when the research solicited cannot be conducted by U.S. institutions or when domestic responses are not competitive. Historically, foreign awards account for about 1 percent of the NIAID research budget. With the increasing competition for NIAID research funding, foreign awards will remain comparatively few in number and will be awarded primarily to scientists in industrialized countries. An exception to this rule is the Tropical Medicine Research Center (TMRC) Program, which provides direct, multidisciplinary research

support to institutions in the tropics. Current TMRCs are located in Salvador, Brazil; Shanghai, China; and Bamako, Mali.

Domestic Research Awards with a Foreign Component

The vast majority of NIAID international research is conducted indirectly through competitive domestic research awards that have a foreign component. Special emphasis programs have been developed in Tropical Medicine, HIV/AIDS, and Tuberculosis to take advantage of research opportunities overseas in these disease areas.

Tropical Medicine is the earliest and most mature of these special programs, which collectively constitute the NIAID International Centers for Tropical Diseases Research (ICTDR) Network. The ICTDR Network consists of (1) Tropical Disease Research Units (TDRUs), which are U.S. institutions conducting multidisciplinary research relevant to the treatment, prevention, or control of tropical diseases; (2) the International Collaboration in Infectious Disease Research (ICIDR) Program, which makes awards to U.S. institutions to collaborate with overseas institutions in tropical and emerging infectious diseases; (3) the TMRCs; (4) NIAID intramural laboratories active in tropical medicine and infectious disease research; and (5) additional U.S. institutions with a critical mass of tropical and emerging infectious disease research grants. In FY 1999 NIAID recompeted and expanded the ICIDR Program and linked it with the new Fogarty International Center (FIC) Assistance in Building Capacity (ABC) institutional research training program.

Initiated in 1994, the NIAID Tuberculosis Prevention Research Center operates through a central research contract located at Case Western Reserve University. The Center coordinates a consortium of U.S. and international institutions (Brazil, Uganda) to carry out a range of high-priority research areas ranging from the most basic to translational research on new or improved treatment and prevention modalities. NIAID recompeted an extended 7-year contract in FY 1999 that will place more emphasis on the development and evaluation of diagnostic products, drugs, and vaccine candidates.

Since its establishment in 1985, NIAID has supported a series of special award mechanisms to carry out research on HIV/AIDS and related problems. These mechanisms and their focus have changed and evolved in response to HIV/AIDS research advantages and resultant research opportunities. NIAID currently supports a master international AIDS contract with Family Health International, which provides support to the U.S. and foreign institutions to conduct HIV/AIDS prevention and vaccine studies at 13 overseas sites in Brazil, Haiti, Kenya, Malawi, South Africa (2), Thailand, Trinidad and Tobago, Uganda (2), Zambia, and Zimbabwe. During FY 2000, NIAID decided to restructure and expand the program to support separate domestic and international sites, which will form an HIV Prevention Trials Network (HPTN) and an HIV Vaccine Trials Network (HVTN). The HPTN consists of 17 U.S. and 13 foreign sites in China, India (2), Peru, Russia, South Africa, Tanzania, Thailand, Uganda (2), Zambia, and Zimbabwe. The HVTN involves eight U.S. and eight overseas sites in Brazil, China, Haiti, India,

Peru, South Africa, Thailand, and Trinidad and Tobago.

Official Bilateral Programs

In addition to regular scientific channels, the United States often develops formal, bilateral scientific agreements with foreign governments. These agreements may be at the vice presidential, Department of Health and Human Services (DHHS), the NIH, or NIAID level. Unless special or supplementary funds are available, these agreements must be carried out within NIAID's budget. During FY 1999, NIAID actively participated in bilateral programs involving Brazil, China, Georgia, Germany, India, Italy, Japan, Poland, Russia, South Africa, and Taiwan. At the NIH level, these programs are coordinated by the FIC. One exception is the U.S.-Japan Cooperative Medical Science Program (USJCMSP), which consists of committees of senior scientists and panels of specialists in high-priority Pacific Rim diseases. Both the Joint Committee and Joint Panels meet annually, alternating countries. Joint Panel meetings are held in conjunction with scientific conferences. Since 1996, the USJCMSP has organized regional workshops on "Emerging Infectious Diseases in the Pacific Rim" held at other sites within the region. Active priority areas are AIDS, acute respiratory infections, cholera and other bacterial enteric diseases, environmental mutagenesis, hepatitis, immunology, leprosy/tuberculosis, nutrition, parasitic diseases, and viral diseases.

International Agencies and Organizations

NIAID has joined in efforts with other organizations to enhance scientific cooperation and collaboration in combating infectious diseases. In March 2000, leaders of pharmaceutical and biotechnology companies, international organizations, foundations, and representatives of the U.S. public health and biomedical research communities convened at the White House to endorse the Millennium Vaccine Initiative. The initiative calls for concerted international action to combat infectious diseases by promoting delivery of existing vaccines in developing countries and by accelerating the development of new vaccines.

U.S. Government agencies often combine resources through interagency agreements to carry out programs or projects of mutual interest. NIAID has supported agreements with the USAID in areas such as malaria and tropical disease control in the Middle East. During FY 2000, NIAID negotiated an umbrella agreement with DHHS for NIH projects supported by the new DHHS-State Department BioTechnology Engagement Program (BTEP). BTEP provides funding for Newly Independent States (NIS) former bioweapons researchers to conduct civilian research. NIAID is also contributing to the Multilateral Initiative on Malaria (MIM) as well as to the International Cooperative Biodiversity Groups Program, designed to foster conservation of biodiversity, spur economic growth in developing countries, and facilitate discovery of pharmaceuticals from natural products. In addition, NIAID staff and awardees are active participants on the scientific boards of and as consultants to international organizations such as the Pan American Health Organization (PAHO/WHO), the World Health Organization (WHO), and UNAIDS.

Acquired Immunodeficiency Syndrome (AIDS)

Since the emergence of AIDS in 1981 as a deadly global infectious disease, considerable progress has been made in understanding AIDS: how HIV attacks the immune system to cause disease and how to intervene therapeutically. Researchers have developed new techniques to detect HIV in blood and tissue and have identified powerful new antiviral therapies to suppress the virus and delay disease progression and death. New therapeutic regimens that include potent protease inhibitors, commonly referred to as highly active antiretroviral therapy or HAART, have greatly improved the quality of life of many HIV-infected people in the United States and have led to a dramatic decline in AIDS-related deaths.

Despite these scientific advances, the number of AIDS cases continues to grow worldwide, decimating parts of the developing world. In some African countries, the prevalence of HIV has reached 10 to 30 percent in adults of reproductive age, and life expectancy in some countries has dropped as much as 20 years since 1990. As of December 2000, there were 36.1 million people (34.7 million adults and 1.4 million children) living with AIDS worldwide. More than 70 percent of these people live in sub-Saharan Africa, and another 16 percent live in South and Southeast Asia.[1]

HIV has become one of the greatest threats to global health. It is unique in its devastating impact on the social, economic, and demographic underpinnings of development and, according to the United Nations and the U.S. National Security Council, poses security concerns.

To address the global impact of AIDS, NIAID supports a broad array of domestic and international AIDS research and collaborates with more than 40 countries through investigator-initiated research grants and through its multicenter prevention, vaccine, and therapeutic research networks.

Vaccine Research

An HIV vaccine that is simple to administer, inexpensive, and induces long-lasting immunity against most HIV subtypes is the ideal prevention strategy and NIAID's highest priority. To accelerate vaccine development worldwide, NIAID recently established the HIV Vaccine Trials Network (HVTN), which provides a global infrastructure for clinically based research and development (see Vaccine Research and Development under Selected Scientific Areas of Interest, page 68).

This year, NIAID-supported researchers completed the first African HIV/AIDS preventive vaccine trial in Uganda. This phase I study was conducted through the HIV Network for Prevention Trials (HIVNET) to evaluate the safety and immunogenicity of ALVAC vCP205, a weakened canarypox virus that has been genetically altered to contain selected HIV genes. The study was also designed to determine whether or not this vaccine could generate immune responses against different types or strains of HIV. This is important because different types of HIV are found in different geographic regions. The vaccine did generate HIV-specific cellular immune responses (specific defense cells that attack infected cells), and because it was a broad-based response, at least in some volunteers, vaccines of this type may help protect against various types of HIV. In addition, by successfully completing this trial in Uganda, researchers in Uganda gained HIV

vaccine trials experience, which will lead the way for conducting international vaccine trials in the future.

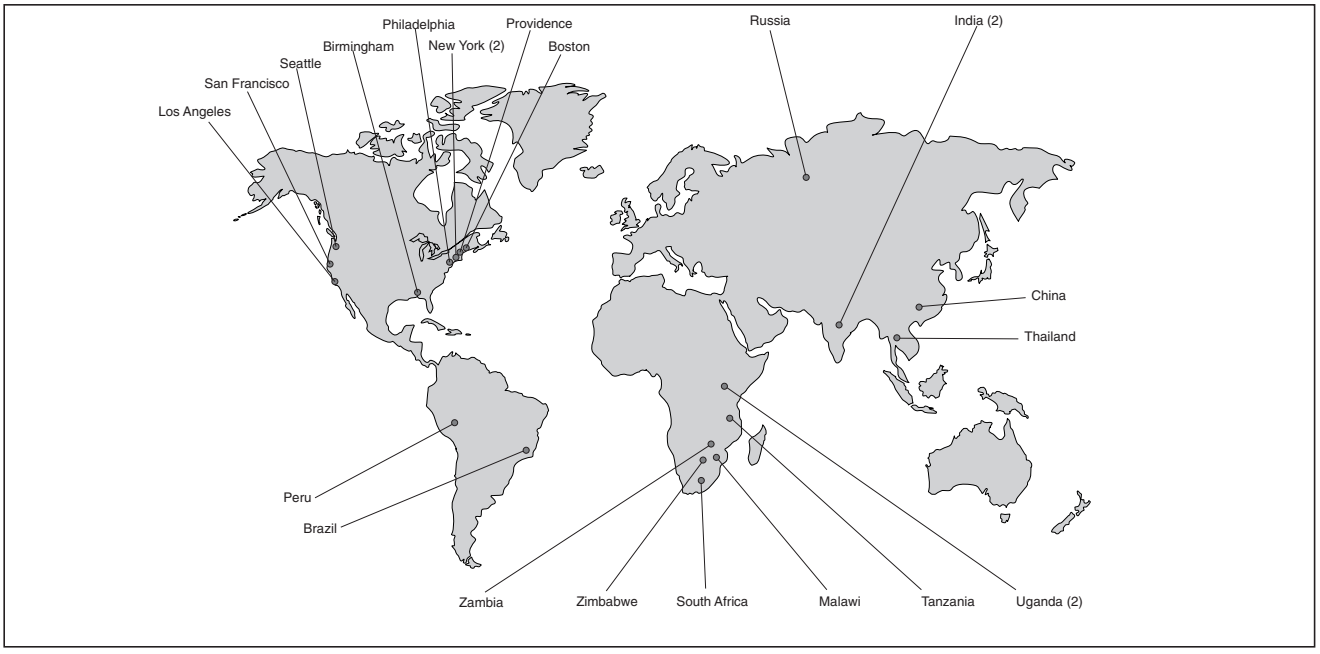
Two phase II vaccine trials (HVTN 203 and HVTN/HIVNET 026) will evaluate the safety and immunogenicity of a canarypox-HIV vaccine (Aventis Pasteur vCP1452) with and without an HIV envelope subunit boost. HVTN 203 is being conducted at domestic U.S. sites and will use the VAXGEN B/B product as a boost. HVTN 026, scheduled to begin in 2001, will be conducted in the Caribbean (Haiti and Trinidad/Tobago) and South America (Brazil) and will use the VAXGEN MN boost. These trials will be the third (HVTN 203) and fourth (HVTN 026) Division of Acquired Immunodeficiency Syndrome-sponsored phase II preventive HIV vaccine trials as progress continues toward the goal of a phase III efficacy trial.

Nonvaccine Prevention Research

Since the first HIV vaccine may only be partially effective, successful prevention measures will likely require a combination of interventions. Also, since it is expected to take several more years to develop an effective vaccine, it is important to develop other promising interventions as rapidly as possible.

This year, NIAID completed the establishment of the HIV Prevention Trials Network (HPTN) to develop and test promising nonvaccine strategies to prevent the spread of HIV/AIDS. This global initiative constitutes NIH's largest comprehensive multicenter network dedicated to HIV prevention research and is also supported by the National Institute for Child Health and Human Development (NICHD), the National Institute on Drug Abuse (NIDA), and the National Institute of

NIAID HIV Prevention Trials Network Domestic and International Sites



Mental Health (NIMH). The HPTN will test the efficacy of promising biomedical/ behavioral interventions for the prevention of HIV, including the following:

- Drugs and/or vaccines that are practical and easy to use to prevent mother-to-infant HIV transmission, including during breastfeeding;
- Microbicides, substances designed for vaginal or rectal use, to prevent sexual transmission of the virus;
- Interventions to reduce behavior that exposes people to HIV;
- Programs to curb the spread of HIV by reducing intravenous drug abuse;
- Measures to control other sexually transmitted diseases (STDs) and thereby decrease the risk of co-infection with HIV; and
- Antiretroviral therapy (ART) that may reduce the spread of HIV from infected persons to their partners.

The HPTN includes 16 domestic sites and 14 international research sites located in Africa (Malawi, South Africa, Tanzania, Uganda [2], Zambia, and Zimbabwe), Asia (China, India [2], and Thailand), Europe (Russia), South America (Brazil, Peru), as well as an operations center, a central laboratory, and a statistical and data management center.

Worldwide, sexual relations between men and women and HIV transmission from mother to infant during pregnancy, at the time of delivery, or through breastfeeding are the most common sources of HIV transmission. Important progress has been made over the past year to advance our understanding of transmission between adults and from mother to infant. Recent findings include the following:

- Identification of a direct correlation between the level of HIV in the blood and the rate of transmission of HIV through heterosexual sex (see text box insert on page 51);
- Stronger evidence that early circumcision may reduce men's risk of HIV acquisition during unprotected sexual contact later in life;
- Analysis of the etiologic agent for genital ulcer disease and the potential role of medications that may suppress outbreaks of herpes simplex type-2 virus (HSV-2) in reducing susceptibility to STDs; and
- Further information on the effectiveness of nevirapine when given to mothers and their newborn infants and its continued benefit in reducing HIV transmission through the first year of life, even with breastfeeding.

Mother-to-Infant Transmission of HIV

In early 1994, administration of zidovudine (AZT) used during pregnancy and delivery in the AIDS Clinical Trials Group (ACTG) study 076 was shown to be extremely effective in preventing perinatal transmission. Although it is now the standard of care for HIV-infected women in the United States, it is too expensive and impractical for widespread use in developing countries, where many women do not receive prenatal care. Shorter courses of AZT that are effective in reducing

mother-to-infant transmission of HIV are still too expensive for widespread use.

In 1999, researchers in Uganda and the United States reported the results of HIVNET 012, which showed that a simple nevirapine regimen given to mothers and their newborn infants could reduce mother-to-infant transmission of HIV by about 50 percent compared with short-course AZT. Recently, this same study team reported that while some new HIV infections occurred in infants as a result of breastfeeding, the overall benefit of this low-cost intervention was maintained through the first year of life. These same investigators reported that 23 percent of a small subset of the mothers in this study had evidence of nevirapine resistance 6 weeks after they had received a single dose of nevirapine; however, recent long-term follow-up assessments have shown that nevirapine-resistant strains cease to be detectable by 12 months. Current research is focused on assessing the duration of this resistance in populations in Africa and the United States to better understand the impact on maternal health and prevention of maternal-infant HIV transmission.

Knowledge about the extent and duration of risk of HIV transmission through breastfeeding is essential for advising HIV-infected mothers, formulating public health policy recommendations, and planning interventions that effectively interrupt transmission during breastfeeding. This is particularly important now that studies have shown that *in utero* and intrapartum HIV transmission can be curtailed by about 50 percent when short-course ART is used in late pregnancy and labor. NIAID-supported researchers recently conducted a study in urban Malawi, Africa, that measured the frequency, timing, and risk factors for the transmission of HIV through breastfeeding. The results show that the risk of HIV transmission to an infant is highest in the early months of breastfeeding but is present for as long as an HIV-infected mother breastfeeds her child. Because alternatives to breastfeeding are often scarce, unsafe, or culturally unacceptable, early weaning may not be feasible as a worldwide strategy to address this issue. NIAID therefore is planning a number of studies that will assess whether the use of low-cost antiviral regimens administered to infants during the first 6 weeks to 6 months of breastfeeding reduces mother-to-infant transmission of HIV.

New Drug Therapies

A major goal of NIAID intramural researchers and their collaborators is to discover new therapies for AIDS that are less expensive and/or less toxic than current therapies and therefore have the potential for more widespread use. Several new approaches are under study in NIAID's Division of Intramural Research (DIR). For some HIV-infected patients whose plasma levels of virus have fallen to undetectable levels while on HAART, it may prove feasible to move from a continuous HAART regimen to intermittent therapy in which an individual discontinues then resumes HAART in a preplanned, cyclic fashion. This cyclic approach to treatment, known as structured intermittent therapy, might enable an HIV-infected person to have regular HAART-free periods while maintaining a minimal viral load and adequate levels of CD4+ T cells. Much more research needs to be done, but preliminary studies suggest this strategy could potentially reduce

total time on HAART in any given period by as much as 30 to 50 percent, thereby reducing HAART-related toxicities and costs while improving patients' adherence to therapy.

NIAID DIR researchers, along with other scientists around the world, are also conducting trials of immune-based therapies, such as interleukin-2 (IL-2), that can be administered in conjunction with antiretroviral therapy. NIAID's long-term basic research into the function of IL-2 in the immune system and into its possible use in HIV therapy has led to promising results in a recent clinical trial that was the first study to suggest a positive effect of IL-2 on viral load. Further studies by DIR investigators as well as two large international studies are ongoing to clarify the affect of IL-2 on viral load and CD4+ counts and to assess long-term clinical outcomes.

Amount of HIV in the Blood Predicts Risk of Heterosexual Transmission

Heterosexual transmission is the principal route of HIV transmission in many parts of the world, including sub-Saharan Africa, which accounts for more than 70 percent of people living with HIV/AIDS worldwide.

NIAID-supported scientists analyzed retrospective data from 415 HIV serodiscordant couples (where one partner was HIV infected) in Uganda and found a direct correlation between the level of HIV in the blood and the rate of transmission of HIV to sexual partners. With every tenfold rise in the concentration of HIV in the bloodstream, the risk of transmission more than doubled. In addition, no one who had fewer than 1,500 copies of HIV RNA per milliliter of blood transmitted the virus to his or her partner.

Antiretroviral therapy (ART) was not available in this study, so low viral load was the result of effective control of HIV by the individual's immune system. These data suggest that using ART to lower viral load may also reduce the risk of sexual transmission. Moving from this finding to developing effective ART interventions will require the identification and ethical evaluation of low-cost, feasible approaches to disseminating ART in resource-poor settings.

Malaria

Malaria continues to pose a tremendous public health burden for people living in the tropics, particularly in Africa. Globally, malaria causes over 1 million deaths each year, primarily in children. According to WHO, 300 to 500 million new cases of malaria occur annually.[2] The situation is worsening, as drug-resistant strains of the most virulent form of the malaria parasite, *Plasmodium falciparum,* have spread to most endemic regions.

Malaria research at the NIH dates back to the 1930s, a time when malaria was a major public health problem in the United States. NIAID is currently one of the world's leading supporters of malaria research. NIAID activities in malaria include a broad portfolio of research on drug development, pathogenesis, vaccine development, epidemiology, and vector control, conducted by scientists at institutions throughout the United States, including NIAID's own intramural laboratories.

NIAID intramural researchers and their colleagues, after more than a decade-and-a-half-long search, have identified the gene that makes the most deadly malaria parasite resistant to chloroquine, the former mainstay, low-cost antimalarial drug. A single gene on chromosome 7 of *P. falciparum* holds the key, and tiny mutations in this gene, known as *pfcrt*, associate completely with chloroquine resistance in parasite lines from affected areas in Asia, Africa, and South America. Discovering how the protein encoded by this gene confers chloroquine resistance is helping investigators understand how modifications of chloroquine could work against the parasite. These studies raise the possibility that chloroquine, perhaps in combination with other agents, could continue to be an important antimalarial drug.

To complement laboratory-based research, NIAID-supported investigators are conducting clinical and field-based studies of malaria in endemic regions, including Brazil, Cameroon, Ghana, Indonesia, Malawi, Mali, Papua New Guinea, and Thailand.

In 1997, the Institute developed a multiyear plan to accelerate research on malaria vaccine development. The plan emphasizes the following:

- Improved access to well-characterized research materials,
- Discovery and preclinical testing of new vaccine candidates,
- Production and evaluation of candidate vaccines, and
- Clinical research and preparation for clinical trials in endemic areas.

As first steps in implementing this plan, NIAID established a repository of well-characterized malaria research reagents, expanded efforts to sequence the genomes of human and rodent malaria parasites, and expanded current malaria vaccine production and evaluation efforts through collaborations between intramural and extramural scientists.

NIAID initiated several new programs in FY 2000, including the following:

- Sites in Ghana and Mali in West Africa, supported by contracts under the "Malaria: Clinical Research and Trial Preparation

Sites in Endemic Areas" initiative, began work in FY 2000. Whereas clinical studies in Mali are already under way, investigators in Ghana are establishing an infrastructure and recruiting personnel to support expanded clinical studies. The on-site resources will support multidisciplinary clinical and field-based research necessary to facilitate conduct of clinical trials of interventions, particularly vaccines against malaria.

- In response to a request for applications (RFAs) to support research into "Enhancing Vaccine-Elicited Protective Immunity in Malaria," NIAID made three new awards in FY 2000 that will further our understanding of the malarial immune response and provide insights into vaccine design. The three awards were made to New York University, the Johns Hopkins University, and the Walter and Eliza Hall Institute.

- Under another RFA entitled "Human Immune Resistance to Malaria in Endemic Areas," NIAID-supported programs in Cameroon, Kenya, and Papua/Indonesia initiated studies in FY 2000 to identify immunologic correlates of protection that will facilitate evaluation of candidate vaccine antigens and will accelerate vaccine development.

- In February 2000, a Memorandum of Understanding was signed by NIAID, the Foundation for the National Institutes of Health, and the Malaria Vaccine Initiative (MVI) to speed the development of a malaria vaccine. Established in 1999 by a grant from the Bill and Melinda Gates Foundation, the MVI will work with NIAID to develop joint work plans for targeted malaria research activities.

- NIAID also recently awarded a 7-year contract to Science Applications International Corporation (SAIC) for malaria vaccine production and support services. The contract will support the transition of new malaria vaccine candidates from discovery in the laboratory to clinical trials.

- In FY 2000, through its new Challenge Grants program, NIAID funded two grants in malaria research. The first grant, awarded to researchers at GlaxoSmithKline Pharmaceuticals, will develop a pediatric indication for tafenoquine, a promising new drug already under investigation for preventing malaria in adults. This research will be done in collaboration with scientists at the Walter Reed Army Institute of Research. A study also will be conducted on the ability of tafenoquine to block transmission of the malaria parasite. The second grant was awarded to Pfizer Pharmaceuticals investigators, who will team with another group of military researchers at Walter Reed Army Institute of Research to study azithromycin for treating malaria. NIAID is a founding member of the Multilateral Initiative on Malaria (MIM), a consortium of research funding agencies created to improve global collaborations in malaria research. MIM works closely with the World Health Organization's Roll Back Malaria Program and others to ensure that research findings are applied to improve malaria control.

New Malaria Research Facility Dedicated in Mali, West Africa

A new malaria laboratory facility was recently dedicated at the University of Mali in Bamako, Mali, West Africa, to promote malaria research, especially the development of effective malaria vaccines. Representatives from the National Institute of Allergy and Infectious Diseases (NIAID) as well as the U.S. Ambassador to Mali, the director of the U.S. Agency for International Development (USAID), the Mali Minister of Health and the Minister of Higher Education, and other dignitaries participated in the dedication ceremonies.

NIAID has been a longstanding supporter and collaborator of Malian scientists. "The Mali facility is a critical part of NIAID's efforts to combat malaria," says Thomas J. Kindt, Ph.D., director of NIAID's Division of Intramural Research (DIR). "The availability of a state-of-the-art research center in an endemic region provides an invaluable base for studies of the disease, its vector, and its causative agent at every level. We hope that the MRTC [Malaria Research and Training Center] will continue to provide a base not only for NIAID-funded scientists and their Malian counterparts, but also for committed health professionals from all over the world."

The labs are part of the MRTC, which opened in 1989. The MRTC works closely with the Malian Ministry of Health, as well as with the National Malaria Control Program. The new facility will house new and ongoing research and training programs supported by NIAID's DIR, the USAID, NIAID's Division of Microbiology and Infectious Diseases (DMID), the NIH National Center on Minority Health and Health Disparities, the NIH Fogarty International Center, the World Health Organization (WHO), and the National Aeronautics and Space Administration (NASA). The new building, which has recently been wired for Internet service, contains two large labs, a conference room, a library, and several classrooms. The benefit of the MRTC program is that Malian scientists carry out the research.

The MRTC labs conduct a broad range of research activities, including studies on the basic epidemiology of disease. Current MRTC program objectives include the detection of parasite resistance to antimalarial drugs and clinical and field-testing of malaria vaccine candidates.

Parasite resistance to antimalarial drugs is a serious concern. Scientists have recently developed a series of tests that rapidly detect resistance in malaria parasites. Researchers are also studying the role of hemoglobin C in the prevention of malaria. Studies in village populations have found that people with high concentrations of hemoglobin C in their blood are more resistant to the malaria parasite and less likely to develop or die from serious disease. Researchers are also developing field sites for the eventual testing of candidate malaria vaccines. They are collecting data on seasonal changes that indicate when most people become infected with malaria, studying the severity of these infections, and determining how a vaccine would best be tested in a human population.

The new labs, primarily devoted to supporting malaria vaccine research and the testing of vaccine candidates, will be an important collaborating facility for DIR's Malaria Vaccine Development Unit located in Maryland, as well as for other NIAID-supported investigators.

Although currently there is no vaccine available for the prevention of malaria, two promising vaccine approaches are being investigated at the MRTC: a blood-stage parasite vaccine and a transmission-blocking vaccine. A blood-stage parasite vaccine attacks the stages of the parasite that cause disease and death, whereas a transmission-blocking vaccine prevents the transmission of malaria via mosquitoes from an infected person to a noninfected person.

MRTC researchers also take an active role in the control of malaria in village populations by stressing better protocols for the treatment of sick children. Outreach efforts have been very successful in teaching parents to seek appropriate medical treatment for their children, thereby reducing mortality rates and the spread of disease.

In addition to NIAID support, the MRTC labs receive funding from several other international and U.S. agencies, organizations, and universities. For example, researchers supported by NIAID, NASA, and the National Oceanic and Atmospheric Administration are using geographic information systems to detect climactic conditions that affect mosquito populations and disease prevalence. By analyzing satellite imagery, scientists can identify such conditions, including humidity, moisture, and areas of water, that attract mosquitoes and increase the potential for disease outbreaks. "Both climate and remote sensing will be used to predict malaria because climate brings water, water brings mosquitoes, and mosquitoes bring malaria," says Dr. Gwadz. In other studies supported by NIAID, WHO, and other foundations, scientists are in the preliminary stages of studying the possible genetic alteration of mosquitoes. Theoretically, scientists would remove the disease-causing properties of the mosquito and then reintroduce the modified mosquitoes into the environment, thereby replacing "bad" mosquitoes with "good" mosquitoes. However, Dr. Gwadz cautions, "This is a very long-range approach with many difficulties. It would not replace or compete with a vaccine strategy, but be part of an integrated malaria control program."

The MRTC is currently upgrading its Internet connection to direct satellite uplinks, which are much faster and more dependable than the local connections. This direct link to the NIH campus will enable Malian researchers to collaborate and exchange data with researchers in Bethesda, Maryland. The MRTC is also developing a wireless network to link the most remote field research clinics to the Internet. This will allow voice, fax, and e-mail communications and database updates from any location within 1,000 kilometers of Bamako, Mali.

The new MRTC lab is a unique research facility that provides the proper tools, resources, and technology to scientists who can then carry out malaria research in their native countries where the disease is endemic. NIAID's continuing support for the MRTC underscores its commitment to the Mali project and to improving global health.

Government and Industry Team Up to Battle Infectious Diseases Through NIAID Challenge Grants Programs

In September 2000, the National Institute of Allergy and Infectious Diseases (NIAID) launched a new initiative intended to encourage private-sector involvement in attacking several of the world's most deadly infectious diseases. Through its new Challenge Grants program, NIAID has provided matching funds to companies that have committed their own dollars and resources toward the development of new drugs and vaccines against malaria, tuberculosis (TB), influenza, and dengue virus. The Challenge Grants are milestone-driven awards, meaning recipients must achieve predetermined product goals during the development process. Progress will be assessed at each milestone, and decisions will be made on continued project funding. Each award is matched with equal dollars from the recipient company, and the combined contributions will be used to support 3-year projects.

The Challenge Grants program, established through appropriated funds from the U.S. Congress, made awards to eight companies that have established capacities and existing infrastructures to rapidly produce new drugs or vaccines as well as novel design approaches to develop new drugs or vaccines. The respective research projects are described below.

Malaria
Researchers at GlaxoSmithKline Pharmaceuticals will develop a pediatric indication for tafenoquine, a promising new drug already under investigation for preventing malaria in adults. This research will be done in collaboration with scientists at the Walter Reed Army Institute of Research. A study also will be conducted on the ability of tafenoquine to block transmission of the malaria parasite, preventing it from passing from person to person.

Investigators from Pfizer Pharmaceuticals will team with another group of military researchers at Walter Reed Army Institute of Research to study azithromycin for treating malaria. To overcome drug resistance, the antimalaria drugs often are used in combination with each other. A number of these combinations contain drugs that cannot be taken by children or pregnant women. Azithromycin is safe in these groups, however, and the researchers will conduct a study of this drug in combination with standard antimalaria agents in Thailand and the Philippines.

Tuberculosis
Scientists at Sequella are directing research on a new generation of antibiotics to battle TB. This team has identified 300 candidate compounds by screening chemical variants of ethambutol, one of the four first-line drugs recommended for treatment of TB. These second-generation molecules will be tested for their efficacy against *Mycobacterium tuberculosis* so more potent treatment options can be developed.

Another group of researchers at GlaxoSmithKline Pharmaceuticals will investigate another class of TB drugs by modifying thiolactomycin, a compound that blocks an important metabolic process in certain bacteria and parasites. This drug class should circumvent existing antibiotic-resistance mechanisms of bacteria, making it a promising approach to treating multi-drug-resistant (MDR) TB. In addition, because thiolactomycin blocks a biochemical pathway common to many microbes, it may be a promising drug for other diseases such as drug-resistant *Staphylococcus* and *Enterococcus* infections, malaria, and trypanosomiasis.

Research on a TB vaccine is also being explored at Corixa Corporation, where investigators are conducting preclinical and clinical testing of new candidate vaccines produced using *M. tuberculosis* proteins. These proteins will be tested in animals for their ability to stimulate an appropriate immune response, and then several of these proteins will be combined into candidate vaccines for further testing.

Influenza
To develop a better vaccine for use against future influenza pandemics, Aviron researchers are working to develop a weakened live influenza virus vaccine and to evaluate new mechanisms of production. The development of a vaccine that can be administered as a nasal mist instead of a shot also is being explored, making it a promising option for widespread distribution and use.

Aventis Pasteur scientists will develop a technology that will allow the rapid engineering and production of specific influenza viruses by using a new DNA-based system to produce influenza vaccine candidates. The goal is to produce four new vaccines for testing in clinical trials and to establish that the use of this new system can shorten the response time needed to produce vaccines against pandemic influenza viruses.

Current influenza vaccines are grown in chicken eggs, which may be in short supply during an influenza pandemic. Therefore, alternatives must be developed to protect the world's population. Novavax has been awarded a grant to produce several non-egg-grown influenza vaccines.

Dengue
OraVax researchers will help develop a vaccine against dengue viruses whereby a proven yellow fever vaccine will be used as the backbone for the new vaccines. By replacing a yellow fever gene with genes from the four dengue serotype viruses, chimeric candidate vaccines will be produced and made ready for initial clinical trials.

Tuberculosis

NIAID plays a lead role in the NIH tuberculosis (TB) research program. From 1992 to 2000, NIAID has continued to increase its TB research portfolio. This action is in response to ongoing concern about increasing worldwide case rates and the development of multi-drug-resistant strains of *Mycobacterium tuberculosis*, the pathogen that causes TB. The World Health Organization (WHO) estimates that there are approximately 8 million new cases and 2 million deaths from TB each year, making TB the leading infectious cause of death from a single pathogen worldwide. It kills more people than AIDS and malaria combined. Approximately one-third of the world's population is infected with *M. tuberculosis*. Moreover, it is estimated that between 2000 and 2020, nearly a billion people will be newly infected, 200 million people will get sick, and 35 million people will die from TB if we do not significantly improve our ability to control this disease.[3] NIAID supports a broad TB research program, primarily through its extramural Division of Microbiology and Infectious Diseases (DMID), with particular emphasis on the following areas:

- Basic biology, immunology, and pathogenesis of TB in animal models and humans;
- The latent (persistent) state in TB infection and reactivation of disease;
- Drug, vaccine, and diagnostic development;
- Development of improved tools for epidemiology; and
- Mycobacterial genomics and postgenomic analyses.

NIAID also supports related whole genome-sequencing efforts, including the sequencing and annotation of the complete *M. tuberculosis* genome (recently completed), *M. avium* genome (under way), and *M. smegmatis* genome (recently initiated). The availability of these genome sequences will improve our understanding of the basic biology and pathogenesis of mycobacterial diseases and stimulate development of new diagnostic tools, vaccine candidates, and drug therapies.

Contracts issued by DMID and the Division of Acquired Immunodeficiency Syndrome (DAIDS) are used to support and promote research in TB. The contract mechanism provided *M. tuberculosis*-derived research reagents and an animal model TB candidate vaccine screening service, established a multidisciplinary Tuberculosis Research Unit, and evaluated large numbers of candidate drugs for *in vitro* and *in vivo* activity against *M. tuberculosis*. NIAID has established a chemical database to serve as a reference for these drug-screening results and to stimulate the design and synthesis of new candidate drugs. A clinical trials network is evaluating existing drugs approved for other clinical indications, and the National Cooperative Drug Discovery Groups-Opportunistic Infections was expanded to search for new drug targets in *M. tuberculosis*. Increased funding through Small Business Innovative Research grants has also promoted development and evaluation of new diagnostic tests for *M. tuberculosis*.

The Division of Allergy, Immunology and Transplantation (DAIT) supports a number of individual research projects concerned with basic mechanisms of immunity to *M. tuberculosis*. DAIT's goals and objectives

with respect to research on *M. tuberculosis* are as follows:

- Encourage expanded research to enhance the effectiveness of the immune attack on intracellular pathogenic organisms such as mycobacteria, with emphasis on killer T-cell stimulation and interaction with cells harboring intracellular pathogens;

- Promote vaccine-relevant research to identify dominant mycobacterial antigens and novel adjuvants that induce protective cellular immune responses;

- Promote research on the development of immunologic reagents for early diagnosis and monitoring of disease; and

- Support research on the identification of genes expressed in immune responses to mycobacterial infection, especially soluble proteins, which might be used in vaccination or in treatment of the disease.

Research topics include T lymphocyte recognition of mycobacterial lipid antigens, the role of various cell populations in combating *M. tuberculosis* infection, and the function of biological oxidants in protective immune processes. DAIT established the Application of Data on HLA and CD1 to the Improvement of Vaccines Program, which is defining peptide antigens of *M. tuberculosis* for use in epitope-based vaccines potentially applicable to diverse human populations. The NIAID Tetramer Facility, which is supported by DAIT, DMID, DAIDS, the Division of Intramural Research (DIR), and the National Cancer Institute, produces peptide-major histocompatibility complex reagents for T-cell detection and has provided more than 500 tetramers to investigators in its first 18 months of operation. Requests include reagents for the study of T-cell responses relevant to many vaccine topics, including intracellular bacterial, viral, and parasite infections, autoimmune diseases, and basic immunobiology. The web site address is http://www.niaid.nih.gov/reposit/tetramer/index.html.

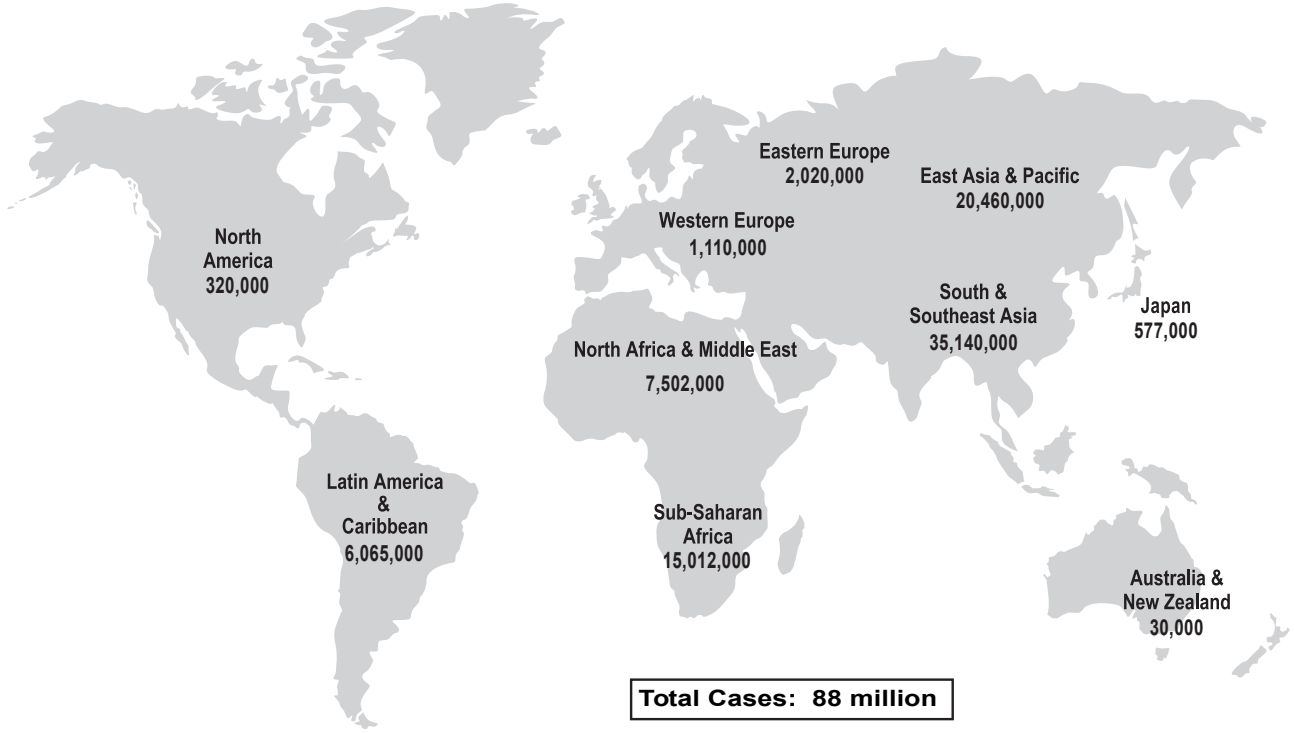
DIR conducts basic research in *M. tuberculosis* at both the Bethesda, Maryland, and the Hamilton, Montana, campuses of NIAID. After contributing to the determination of the genomic sequence of *M. tuberculosis*, DIR investigators are now focusing on unraveling the functions of its various genes. This knowledge is critical to new drug and vaccine development and to understanding the molecular mechanisms involved in the emergence of drug resistance.

DIR's studies of the biochemical, immunologic, and genetic factors that contribute to human susceptibility and pathogen fitness have yielded many important findings that have enhanced the diagnosis and treatment of mycobacterial diseases. Using the most modern technologies, DIR scientists are also working on a number of different approaches to understand how current antitubercular chemotherapy works. They will use this information to develop new and improved therapies and therapeutic approaches. Individual projects are aimed at understanding the mode of action of existing front-line antituberculars such as isoniazid and ethambutol, two drugs that form the backbone of modern short-course chemotherapy for TB. This knowledge is translated into screens for second-generation antituberculars based on the same basic mechanism of action.

DIR scientists are involved in a collaborative effort to understand the mode of action of a new series of compounds, called nitroimidazopyrans, that were developed by the PathoGenesis Corporation of Seattle, Washington. These are the first new compounds that have been put forward for preclinical testing and evaluation against TB since the rifamycins were introduced in 1972. The compounds were shown to have significant activity against bacteria that are not actively replicating, a finding that has important implications for the one-third of the world's population that harbor latent bacilli and are at continued risk for the development of active TB.

NIAID's increased support for TB research has resulted in significant advances in our understanding of the basic biology, microbiology, and immunology of TB, which will result in the development of new diagnostic tools, vaccine candidates, and therapeutic strategies to prevent and ultimately cure this devastating disease.

Estimated Cumulative Tuberculosis Cases 1990-1999



Source: Tuberculosis Programme/WHO

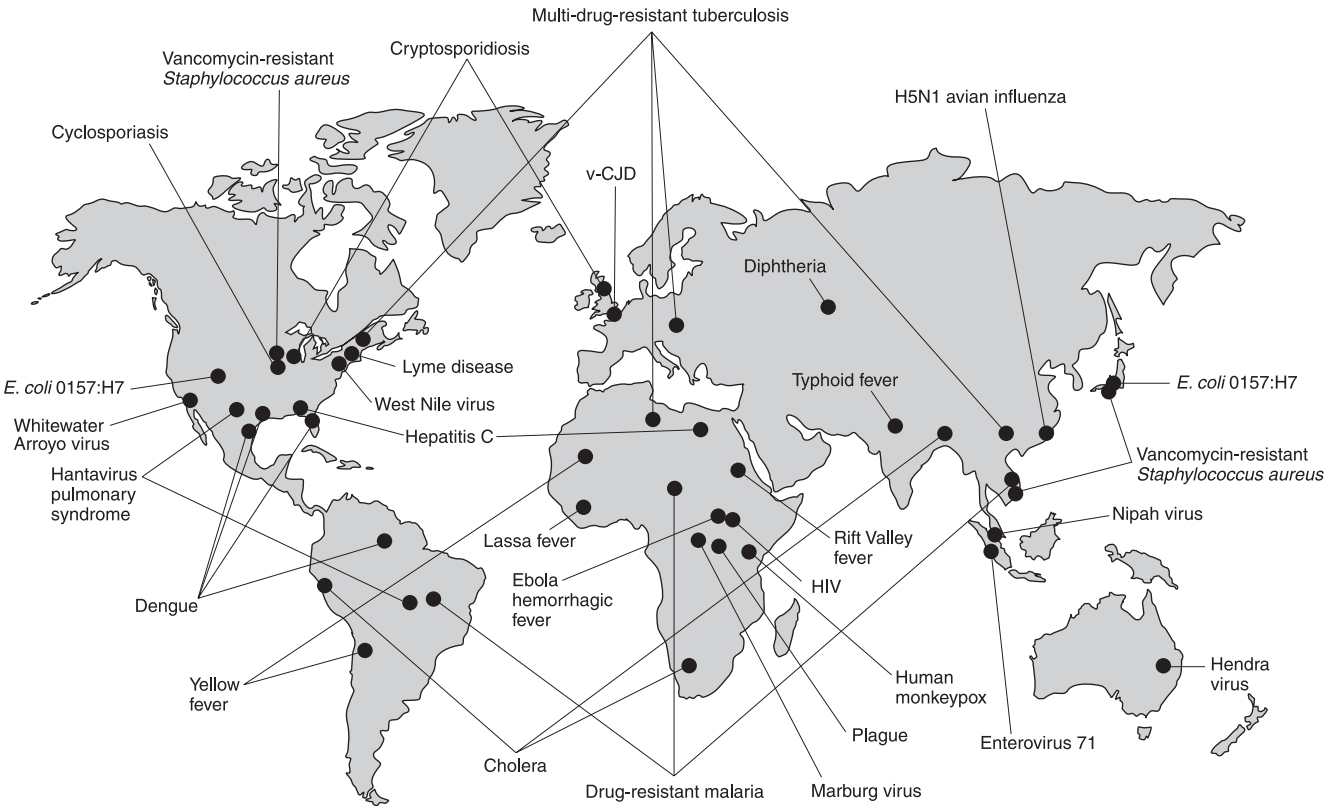
Emerging Infectious Diseases

The control of often deadly infectious diseases is one of the great achievements of the twentieth century. This ability was largely due to fundamental research in the field of microbiology, which laid the foundation for later efforts to develop vaccines and antimicrobial drugs. During the preceding two decades, however, as new human pathogens have been recognized—and previously known pathogens have become drug-resistant—researchers and physicians have come to realize the threat of infectious diseases is far from over; indeed, it remains an unending struggle.

- The KwaZulu-Natal Department of Health in South Africa has reported an increase in the number of cases and deaths of cholera since the start of the outbreak in mid-August 2000. Cholera is endemic to the eastern seaboard of southern Africa, and outbreaks can occur sporadically in any part of the world where water supplies, sanitation, food safety, and hygiene practices are inadequate.

- Worldwide, approximately 2 to 3 million people died from tuberculosis (TB) in 1998, and an estimated 8 million new cases developed. *Mycobacterium tuberculosis* kills more people globally than any other single infectious agent. The duration of standard TB drug therapy (6 to 12 months) and the associated drug toxicities often result in

Examples of Emerging and Reemerging Diseases



decreased patient compliance and allow for the emergence of single- and multi-drug-resistant TB (MDR-TB) strains. Drug-resistant TB is more difficult and vastly more expensive to treat than drug-sensitive TB, and due to inadequate treatment, patients with drug-resistant TB often remain infectious longer than those with drug-sensitive strains. Without additional efforts to control the disease, the incidence of TB is predicted to increase a further one-third over the next decade (1995-2005).[3]

- Seventeen human cases of West Nile virus were reported this year, all in New York City and New Jersey. The virus can cause encephalitis, a brain inflammation. But it is unknown how many people had milder, asymptomatic cases of West Nile, which can feel like the flu, without seeking medical attention. Most confirmed cases tend to be among patients with weaker immune systems, such as the very old or very young. Birds infected with the West Nile virus were reported in several eastern states in 2000 as far south as Virginia, foreshadowing the likely continued emergence of this disease.

Basic and clinical research is critical to the development of a national strategy to confront these microbial challenges. Such research increases our collective understanding of ever-changing microbial populations and permits this new knowledge to be transformed into better diagnostics, vaccines, and therapies. Basic research and research training also are the foundation for surveillance and response activities. NIAID's plan to address gaps in the ability to detect and respond to microbial threats is set out in its *Research Agenda for Emerging Infectious Diseases*, which can be viewed on NIAID's homepage (http://www.niaid.nih.gov/publications/execsum/bookcover.htm).

The *Research Agenda* defines priorities in the following three broad areas:

- Expand the fundamental understanding of infectious agents, human susceptibility and immune responses to them, and the environmental factors that influence their emergence and spread;

- Strengthen the ability to develop and validate new tools to prevent and control infectious diseases; and

- Ensure that support for training and research is sufficient for building and maintaining the scientific expertise and resources needed to meet future emerging disease threats.

Research on emerging and reemerging infectious diseases is a high priority for NIAID and, together with global health research, comprises one of the four cornerstones of NIAID's *Strategic Plan* for biomedical research.

During 2000, NIAID supported research initiatives on emerging infectious diseases in multiple areas, including hepatitis C, TB, emerging viral infections, and malaria. NIAID funded three awards in response to a joint request for application (RFA) with the National Institute of General Medical Sciences on the "Evolution of Infectious Diseases." These grants are focused on malaria, rabies, dengue, and enteric infections. NIAID also cosponsored a joint RFA with the Fogarty International Center, the National Institute of Environmental Health Sciences, the National

Institute of General Medical Sciences, and the National Science Foundation on the "Ecology of Infectious Diseases." Under this solicitation, 12 awards were made to study the impact of anthropogenic environmental changes on the transmission of infectious agents. The NIAID awards under this program address malaria vectors in Belize, enzootic arbovirus transmission in Peru, and encephalitis transmission vectors in the southeastern United States.

NIAID's International Collaboration in Infectious Disease Research (ICIDR) program provided supplemental funds in FY 2000 for a joint United States/South American project focused on surveillance studies designed to monitor the appearance of birds infected with the West Nile virus in the Yucatan Peninsula. Study sites were established in nature preserves in the Yucatan, which can be rapidly accessed to assess the potential for trafficking of the West Nile virus in Central America.

NIAID-supported scientists have also determined the entire order of chemical building blocks that make up the DNA of the deadly cholera bacterium *Vibrio cholerae*, an ancient infectious foe. This breakthrough will likely aid further research efforts leading to the development of new vaccines and therapies.

NIAID continues to collaborate with the Fogarty International Center on the support of a program on International Training and Research on Emerging Infectious Diseases to address research training needs related to emerging and reemerging infectious diseases in developing countries. In addition, NIAID continues to participate in interagency governmental efforts, such as the National Science and Technology Council's Committee on International Science, Engineering, and Technology.

In addition, through its new Challenge Grants program, described on page 55, NIAID has funded grants in emerging infectious disease areas such as dengue, influenza, and TB.

NIAID has recently funded a grant to develop a West Nile virus vaccine using a new method developed for production of a Japanese encephalitis vaccine (a related flavivirus). This method uses the yellow fever virus vaccine (a closely related flavivirus) as a vectoring backbone.

The extramural Virology Branch of NIAID's Division of Microbiology and Infectious Diseases is funding two projects that are studying aspects of chronic wasting disease (CWD) transmission (prion entry, trafficking, and neuroinvasion). NIAID's Division of Intramural Research (DIR) investigators are conducting studies that may lead to a new treatment for prion diseases, such as Creutzfeldt-Jacob disease (CJD), and are planning experiments to determine the transmissibility of the CWD agent using animal models.

DIR scientists are working on a strategy for constructing attenuated chimeric viruses bearing the protective antigens of various highly virulent tick-borne flaviviruses. This strategy will be applied to construct viruses containing sequences from the mosquito-borne West Nile flavivirus and from the distantly related dengue type 4 virus to investigate the protective capacity of chimeric viruses against West Nile encephalitis.

And finally, to enhance the capacity to deal with the challenges posed by emerging diseases, DIR is constructing new biosafety level three (BSL-3) laboratories in Rockville and Bethesda, Maryland, and in Hamilton, Montana. These laboratories will give DIR the capability to conduct BSL-3 animal studies as well as laboratory research on infectious agents such as multi-drug-resistant *Mycobacterium tuberculosis*. Research programs on pathogenic microorganisms, including *Borrelia, Yersinia*, the influenza virus, and agents of transmissible spongiform encephalopathies, will be continued and expanded.

NIAID is supporting research in prion diseases, an area that is increasing as an emerging health disease threat. Prions are abnormal proteins believed to be responsible for transmissible spongiform encephalopathies, a group of rare, fatal disorders that slowly destroy the brain and nervous system. These diseases include bovine spongiform encephalopathy (BSE or "mad cow disease") in cattle, scrapie in sheep, chronic wasting disease (CWD) in deer and elk, and Creutzfeldt-Jacob disease (CJD) in humans. Mad cow disease was first detected in Britain in the late 1980s, and a growing number of cases have been reported in Europe. The disease is believed to be the result of feeding grazing animals the ground-up remains of infected animals.

A new variant of CJD appeared in England in 1996, coinciding with a BSE epidemic in that country. As of February 2001, 92 Europeans, including 88 from England, had been diagnosed with variant CJD. Because the new variant closely resembles BSE, health officials believe the disease was spread to humans by consumption of infected beef. In 1997, the FDA banned the use of feed supplements made from cattle by-products, the practice linked to infection of British herds, and in 1999 recommended deferral of blood donors who lived in England for at least 6 months during the epidemic period. Though BSE has not been found in the United States, CWD is prevalent in deer and elk populations in the western United States.

Antimicrobial Resistance

Drug-resistant infectious agents—those that have developed the ability to circumvent the action of antimicrobial compounds—are an increasingly important public health concern. Tuberculosis, gonorrhea, malaria, and childhood ear infections are just a few of the diseases that have become more difficult to treat due to the emergence of drug-resistant pathogens. Antimicrobial resistance is becoming a factor in virtually all hospital-acquired (nosocomial) infections. The impact of antimicrobial resistance includes an increase in the cost of treating infections, the necessity of using more and broader spectrum drugs to clear resistant infections, the development of situations in which no drugs are available for multi-drug-resistant pathogens, and an increase in selective pressure leading to the spread of resistant organisms.

Acquired antimicrobial resistance has been recognized since the introduction of penicillin nearly 50 years ago, when penicillin-resistant infections caused by the common skin bacteria *Staphylococcus aureus* rapidly appeared. Today, hospitals worldwide are facing unprecedented crises from the rapid emergence and dissemination of microbes resistant to one or more antimicrobial agents.

- The most common nosocomial bacteria currently causing bloodstream infections in the United States are coagulase-negative staphylococci, *S. aureus*, and *Enterococcus*. Increases have been documented for methicillin resistance among *S. aureus* (MRSA), methicillin resistance among coagulase-negative staphylococci, and vancomycin resistance in enterococci in intensive care units (ICUs). MRSA, long a problem in ICUs and nursing homes, is an emerging community-acquired pathogen.

- In addition, *S. aureus* strains with reduced susceptibility to vancomycin have been reported in the United States in Illinois, Michigan, Minnesota, Nevada, New Jersey, and New York, as well as in France, Germany, and Japan.

- Increasing reliance on vancomycin has led to the emergence of vancomycin-resistant enterococci (VRE), bacteria that infect wounds, the urinary tract, and other sites. The rate of resistance of VRE in U.S. hospitals increased 24.7 percent between January and December 1999 as compared with the previous 5-year period.[4]

- *Streptococcus pneumoniae* (pneumococci) causes thousands of cases of meningitis and pneumonia, and 7 million cases of ear infection in the United States each year. Multi-drug-resistant pneumococci are common and increasing. Overall, 24 percent of isolates causing invasive disease are resistant to penicillin, with averages as high as 35 percent in some States. Penicillin-resistant isolates also show resistance to other antimicrobial agents.[5]

- An estimated 300 to 500 million people worldwide are infected with the parasites that cause malaria, with 1 million people dying. Resistance to chloroquine, once widely used and highly effective for preventing and treating malaria, has emerged in most parts of the world. Resistance to other antimalarial drugs also is widespread and growing.[6]

- The incidence of multi-drug-resistant tuberculosis (MDR-TB) has increased dramatically in the past decade and is currently present on five continents. Infection with TB in people also infected with HIV is occurring in several regions, in particular Africa and Asia, with negative impact on clinical outcome. Drug-resistant strains are as contagious as those that are susceptible to drugs and often reflect mismanagement of therapy. MDR-TB is more difficult and vastly more expensive to treat, and patients may remain infectious longer due to inadequate treatment.[7]

- Diarrheal diseases cause almost 3 million deaths a year—mostly in developing countries where resistant strains of highly pathogenic bacteria, such as *Shigella dysenteriae, Salmonella typhi*, and *Vibrio cholerae*, are emerging. Worldwide, shigella has progressively become resistant to most of the widely used inexpensive antibiotics. Multiple-resistant strains have occurred in Latin America, Central Africa, and Southeast Asia. *S. dysenteriae* type 1 is now uniformly resistant to almost all first-line agents.[8] There is increasing evidence that the use of antimicrobials in food animals is associated with the emergence of resistance among *Salmonella* and *Campylobacter* isolated from the meat of animals.

In response to this threat, NIAID funds a diverse portfolio of grants and contracts to study antimicrobial resistance in major viral, bacterial, fungal, and parasitic pathogens. NIAID-funded projects include basic research into the disease-causing mechanisms of pathogens, host-pathogen interactions, and the molecular mechanisms responsible for drug resistance, as well as applied research to develop and evaluate new or improved products for disease diagnosis, intervention, and prevention.

In addition, NIAID supports a number of clinical trial networks with the capacity to assess new antimicrobials and vaccines with relevance to drug-resistant infections. Among these are the AIDS Clinical Trials Groups, the Mycoses Study Group, the Collaborative Antiviral Study Group, the Tuberculosis Research Unit, and the Vaccine and Treatment Evaluation Units.

In recent years, NIAID has launched several projects to accelerate research on antimicrobial resistance, to develop products to address this challenge, and to support new clinical trial activities in this area. The Network on Antimicrobial Resistance in *Staphylococcus aureus* (NARSA) provides a repository of resistant bacteria, a registry of case information, and a network of investigators to support and stimulate research in the area of resistant bacterial infections. The NIH initiated the Challenge Grants-Joint Ventures in Biomedicine and Biotechnology Program that seeks to form government and industry partnerships to support therapeutic and vaccine development efforts. A Summit on Development of Infectious Disease Therapeutics was convened with pharmaceutical, biotechnology, and academic collaborators to discuss the state of development of new therapeutics for diseases of public health significance. A request for proposals has been issued to provide support for clinical studies of interventions for serious fungal and health-care-associated resistant bacterial infections.

Finally, NIAID/NIH cochairs an Interagency Task Force on Antimicrobial Resistance with the Centers for Disease Control and Prevention and the Food and Drug Administration; several other Government agencies are also represented on this task force. In June 2000, *A Public Health Action Plan to Combat Antimicrobial Resistance Part 1: Domestic Issues* was released for public comment. The action plan reflects a broad-based consensus of Federal agencies on actions needed to address antimicrobial resistance, which is based on input from constituents and stakeholders, and will serve as a blueprint for specific, coordinated Federal actions. The action plan is available online at CDC's Antimicrobial Resistance web site http://www.cdc.gov/drugresistance/.

Hepatitis C

Hepatitis C is an emerging disease in the United States and worldwide. Before 1990, transfused patients were vulnerable to an unidentifiable liver disease agent(s) known only as non-A, non-B hepatitis. Cloned and sequenced nearly a decade ago, hepatitis C virus (HCV) was identified as the cause of most of these chronic infections. Chronic hepatitis C infection can lead to liver inflammation, cirrhosis, and cancer. HCV remains the leading reason for liver transplants in this country. Today, injection drug users are at highest risk, yet transmission also occurs sexually (greatest with multiple partners), as well as through other mechanisms involving inadvertent exposure to contaminated blood. Rapid improvement in HCV diagnostics has occurred, making the supply of blood and blood products very safe; however, exposure continues at the rate of 30,000 new cases a year. Estimates today indicate that HCV is carried by more than 170 million people worldwide, with 4 million in the United States alone. Approximately 85 percent of those infected become chronic carriers, many of them unknowingly, and manifest no overt signs of liver morbidity for decades while their livers are undergoing active disease progression. Public health costs are probably underestimated at $600 million a year, excluding transplantation. From 8,000 to 10,000 HCV-associated deaths occur annually, and according to the Centers for Disease Control and Prevention, this number is expected to triple in the next few decades, surpassing the death rate due to HIV infection.[9]

NIAID has aggressively pursued the expansion of hepatitis C research through its development of the "Hepatitis C Framework for Progress." With the aid of participating Institutes and Centers, an NIH-wide framework was drafted that incorporates the missions of the participants into a cohesive global plan. The final plan was reviewed by outside experts and signed off by Institute directors prior to forwarding to the NIH Director's Office for final approval. The following research goals were identified in the framework:

- Understanding transmission modes to develop effective intervention strategies;
- Understanding pathogenic mechanisms and disease progression to develop treatments;
- Characterizing hosts' immune responses to infection to develop vaccines and prophylactic measures as well as therapeutic measures;
- Defining viral replication and recovery with therapy as well as developing new therapeutic strategies;
- Investigating clinical manifestations to develop noninvasive methods to evaluate current disease state, to predict outcomes, and to prevent/reverse disease progression; and
- Defining effective prevention and intervention strategies to improve health.

The tools needed to develop these goals include tissue culture systems, small animal models, and well-defined clinical cohorts.

Therapeutics has considerable room for improvement. Current therapies include various forms of interferon alpha and an interferon-ribavirin combination that improves the success rate. Long-lasting forms of

interferon with and without ribavirin are currently in the final stages of development. Unfortunately, these drugs have a significantly lower success rate in patients infected with the viral genotype that predominates in the United States, as well as in African Americans. Other therapeutic targets being addressed include inhibitors of key viral components, such as the polymerase protease, helicase, and internal ribosome entry site, and other viral enzymes critical for replication. NIAID is soliciting Small Business Innovative Research applications to develop small animal models, a key research need.

Vaccine development for HCV will require increased understanding of the protective immune response and of viral immune evasion tactics. These areas can best be studied in individuals with acute (early) infection.

In 2000, NIAID funded six "Hepatitis C Cooperative Research Centers," a network that unites basic and clinical researchers investigating hepatitis C infection and the disease process in an effort to identify new and better means of prevention and treatment. This is the second funding cycle for this program. The six awards include the renewal of all four recompeting sites and funding for two new sites. This multidisciplinary scientific coalition is expanding its investigation of acute and chronic infection caused by HCV. Largely unexplored questions, such as why African Americans respond so poorly to the current standard of care, and unresolved issues, such as how the disease persists unnoticed in the body for decades, will be added to the ongoing studies of the Hepatitis C Cooperative Research Centers. In addition, the initiative will fund three new separate studies conducted independently of the larger centers. These studies include (1) extensive HCV polymerase studies and interferon resistance, (2) addition of IL-2 to the current state-of-the-art therapy for HCV in a clinical trial, and (3) the activation of B cells and subsequent antibody production against HCV.

NIAID's intramural research on hepatitis C recently yielded important findings that begin to explain why so many patients fail to fully recover from hepatitis C infection. In collaboration with scientists from other institutions, DIR researchers found that changes in HCV surface proteins soon after infection enable the virus to evade the immune system. The study showed that the ultimate outcome of a hepatitis C infection is determined during the initial acute phase of disease.

In some patients, the virus remained relatively unchanged following the initial immune response, and those people completely eliminated HCV over several weeks. In most patients, however, genetic HCV variants began to appear in response to the early immune assault. This rapid viral evolution ultimately resulted in chronic infection. Future studies will focus on the types of mutations that assist HCV in avoiding the immune system, and on the types of antibodies produced during the early response. By understanding more about this critical checkpoint in hepatis C infection, investigators hope to develop new tools for hepatitis C treatment and prevention.

Institute and multi-Institute-based HCV efforts and initiatives continue to be a high priority for NIAID.

Vaccine Research and Development

NIAID is the center of vaccine research and development within the Department of Health and Human Services. The Institute's broad research programs on all classes of infectious diseases and their causative agents, together with basic research on the immune system, have nurtured comprehensive, collaborative vaccine efforts among scientists in government, industry, and academic institutions. In setting priorities for vaccine development, NIAID weighs severity of disease, expected health benefits, scientific and programmatic gaps and opportunities, and feasibility, given the status of scientific knowledge about particular diseases and their causative agents.

Vaccine research is conducted both intramurally and extramurally by four NIAID divisions—the Division of Acquired Immunodeficiency Syndrome (DAIDS), the Division of Allergy, Immunology and Transplantation (DAIT), the Division of Intramural Research (DIR), and the Division of Microbiology and Infectious Diseases (DMID)—and by the NIAID Dale and Betty Bumpers Vaccine Research Center (VRC). Directors of these four Divisions and Division representatives comprise the NIAID Interdivisional Vaccine Working Group. This group provides both an advisory and coordinating function for the Institute to strengthen and coordinate collaboration on activities related to vaccine research.

DAIDS recently established the HIV Vaccine Trials Network (HVTN). NIAID's HIV vaccine research program was previously centered in two separate groups: the U.S.-based AIDS Vaccine Evaluation Group (AVEG), which carried out early-stage testing of vaccine candidates, and the HIV Network for Prevention Trials (HIVNET), which conducted domestic and international trials of HIV vaccine and other prevention strategies. AVEG and HIVNET investigators, along with other scientists worldwide, underwent a competitive, peer-reviewed evaluation process during the creation of the new network. The HVTN represents a coordinated, global framework in which to conduct clinical HIV vaccine research both domestically and internationally. Additional detail on the HVTN is provided following Division information under DAIDS.

DMID supports six Vaccine and Treatment Evaluation Units (VTEUs) and several special emphasis sites for clinical research, such as the Enteric Pathogens Research Unit and the Maternal Immunization Group. Both the HVTN and the VTEUs conduct phase I and phase II human trials to evaluate the safety and immunogenicity of candidate vaccines. The VTEUs also conduct large placebo-controlled, multicenter phase III trials of protective efficacy that involve large numbers of volunteers. These units complement each other in that various population groups (e.g., infants, young adults, elderly at-risk individuals) are studied in some units but not in others. Additional detail on the VTEUs is provided in following Division information under DMID.

DAIDS and DMID also have vaccine production contracts that provide opportunities to develop and test vaccine concepts at early stages of development. Infrastructure for regulatory oversight, site monitoring, and data management round out the vaccine-development process. In collaboration with the Fogarty International Center, both Divisions support site

development as well as training in clinical trials. Research supported by DAIT is designed to apply the fundamental principles of immunology to the development of improved vaccines.

In March 2000, former President Clinton convened a meeting with the leaders of industry, foundations, and international organizations to unveil his Presidential Millennium Vaccine Initiative, which encourages partnerships among these different sectors to develop and deliver vaccines for diseases—particularly HIV, tuberculosis (TB), and malaria—for developing countries. In response to this new Presidential initiative, NIAID convened a meeting entitled "Addressing the Presidential Challenge: Vaccines for HIV, Malaria, and Tuberculosis" at the NIH in May 2000. This meeting brought together representatives from academia, industry, and government to address the impediments to vaccine development for the target diseases and to develop new ways to strengthen public-private partnerships. NIAID has developed a related initiative, the "Millennium Vaccine Initiative—Targeted Malaria and Tuberculosis Vaccine Development in the Biotechnology Industry," in response to this meeting and plans to make awards in FY 2001.

Division of Acquired Immunodeficiency Syndrome

As AIDS continues to take its toll globally, the development of a safe and effective vaccine against HIV is critical to worldwide efforts to control the epidemic. Although educational and counseling efforts have had some success, it has become evident that these prevention activities alone are not sufficient to contain the spread of the disease.

Given the overwhelming need for a safe and effective HIV vaccine, former President Clinton challenged scientists to develop a vaccine by the year 2007. The AIDS Vaccine Research Committee (AVRC) and the VRC are key to responding to this challenge. The AVRC, chaired by Dr. David Baltimore, stimulates HIV vaccine research and assists the NIH in developing a comprehensive research program aimed at expediting the discovery and development of a safe and effective vaccine. The VRC will advance multidisciplinary research from basic and clinical immunology and virology through to vaccine design and production, and will bring together intramural scientists from across the NIH. This work will complement the comprehensive extramural research activities of DAIDS.

To hasten HIV vaccine discovery efforts, DAIDS uses a two-pronged approach that emphasizes both fundamental research and traditional empiric-based vaccine evaluation. The first approach strives to design promising vaccine candidates through the discoveries that arise from fundamental research in the fields of HIV pathogenesis, microbiology, immunology, virology, and animal model development. Much of this work is supported by traditional investigator-initiated research grants. In the second approach, which is based on strong scientific rationale, investigators produce and determine the safety, immunogenicity, and eventually the efficacy of candidate vaccines.

Since 1987, more than 3,400 non-HIV-infected volunteers have enrolled in 55 NIAID-supported preventive vaccine studies (52 phase I safety studies; 3 phase II safety and immunogenicity studies) involving 29 vaccine candidates and 12 adjuvants, including viral

subunits, peptides, virus-like particles, DNA vaccines, and live virus vectors as well as combinations of all of these vaccine approaches.

This year, to create a global infrastructure for HIV vaccine trials, NIAID completed the establishment of a new comprehensive, clinically based research and development network with an expanded, integrated clinical research agenda and with both domestic and international components. The HVTN is optimally designed to address the scientific and public health needs and opportunities currently facing the field of HIV prevention science. The network strengthens and expands NIAID's capacity to conduct HIV vaccine studies both domestically and in countries devastated by the AIDS pandemic. It has the capacity to conduct all phases of clinical trials, from evaluating candidate vaccines for safety and the ability to stimulate immune responses (phase I and phase II), to testing vaccine efficacy (phase III), and with U.S.-based units integrated with sites around the globe, the HVTN can expand rapidly to carry out larger scale studies of suitable vaccines.

The HVTN will continue safety and immunogenicity studies of promising vaccine candidates already being tested by the AVEG and HIVNET, and will initiate new studies of novel approaches that may elicit anti-HIV antibodies, cytotoxic T lymphocytes, and other potentially protective immune responses. Once the safety of the candidate vaccine is confirmed and the optimal dosage, regimen, and schedule for administering it is determined, the network will conduct larger efficacy studies. Some of the vaccine candidates and approaches that will be explored include the following:

- Recombinant viral-vectored vaccines (now in phase I and phase II trials), which use non-HIV viruses that are engineered to carry genes for one or more HIV proteins;

- Subunit vaccines, which are purified protein components of the HIV virus, particularly the envelope protein;

- DNA vaccines made from selected genes of HIV;

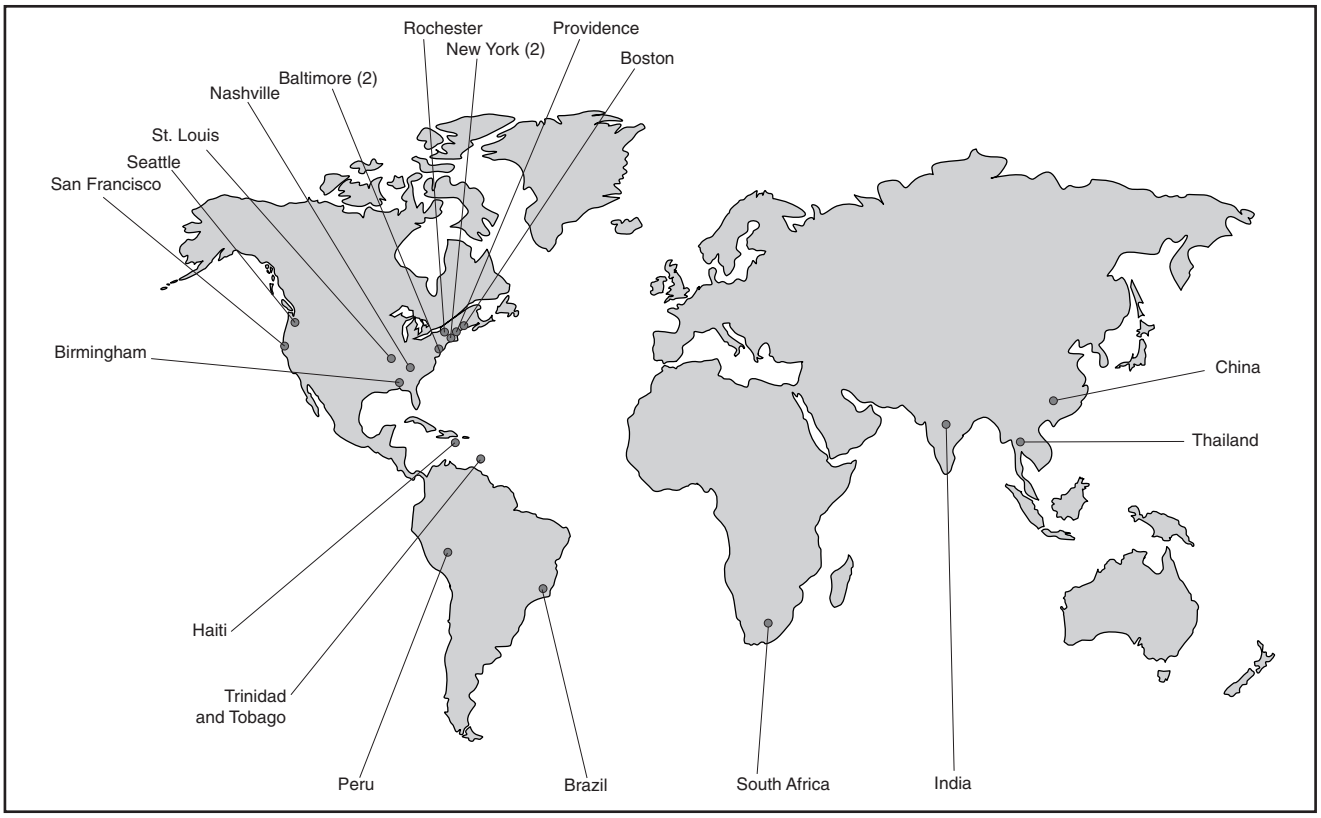
- A combination of approaches, such as a canarypox vector given with a subunit vaccine or a DNA vaccine; and

- Other new viral-vectored vaccines, such as a non-disease-causing Venezuelan equine encephalitis (VEE) replicon suitable for humans and a weakened form of vaccinia virus called MVA.

In addition to an Operations Center, a Central Laboratory, and a Statistical and Data Management Center, the network includes nine domestic sites and eight international sites in Africa (South Africa), Asia (China, India, Thailand), South America, and the Caribbean (Brazil, Haiti, Peru, Trinidad and Tobago) (see map on following page).

To expedite the development of promising HIV/AIDS vaccines for use around the world, NIAID also established four novel public-private partnerships under a program entitled the HIV Vaccine Design and Development Teams (HVDDT). These "teams" tap the different skills and talents of private industry and academic research centers and are given financial incentives to move strong HIV/AIDS vaccine candidates out of the laboratory and into human testing. The program responds

NIAID HIV Vaccine Trials Network Domestic and International Sites



directly to former President Clinton's call to increase public-private cooperation in developing vaccines against globally important diseases such as AIDS, TB, and malaria, and encourages pharmaceutical companies to invest more in AIDS vaccine research by partially offsetting their financial risk.

Division of Allergy, Immunology and Transplantation

DAIT supports research on immunological mechanisms and novel technologies applicable to vaccine design and development. The Division currently funds nearly 100 vaccine-related research projects that aim to increase our ability to rationally manipulate immune responses through better understanding of the underlying molecular, cellular, and systemic aspects of natural host defenses and antigen-specific immunity. Projects include basic studies of innate immune receptors for pathogen molecules, antigen processing and presentation, the development of antibody and cellular responses, and the elaboration of immunological memory. Other topics more immediate to vaccine applications include the development of new adjuvants to enhance immunity, the design of approaches to induce protection in mucosal tissues, and the discovery of novel methods for more effective delivery of immunizing agents.

In FY 2000, DAIT established four new Vaccine Immunology Basic Research Centers that focus on the fundamental aspects of

human protective immune mechanisms in infectious diseases. Through the Human Immunology Centers of Excellence Program, DAIT supports numerous mechanistic studies that will contribute to our basic understanding of human immunity and vaccine responses. In response to the Broad Agency Anouncement "Application of Data on HLA and CD1 to the Improvement of Vaccines," several DAIT-supported projects are now in progress and will focus on hepatitis B, hepatitis C, malaria, TB, and HIV.

An important new area of disease prevention focuses on the use of vaccination approaches to prevent autoimmune diseases. Although no vaccine for any autoimmune disease currently exists, development appears to be feasible based on studies in animal models. Vaccines for autoimmune diseases will be distinct from the vaccines given to prevent infectious diseases. Vaccines for autoimmune diseases will "turn off" a destructive immune response that is directed at the body's own tissues. NIAID, in collaboration with multiple NIH Institutes and the Juvenile Diabetes Research Foundation International, intends to establish a program to focus on development of the knowledge necessary to rationally design and implement strategies to prevent autoimmune diseases, including type 1 diabetes.

NIAID, in collaboration with the National Institute of Diabetes and Digestive and Kidney Diseases and the National Institute of Child Health and Human Development, supports the Diabetes Prevention Trial-Type 1 to test the efficacy of low-dose, parenteral insulin and oral insulin to prevent type 1 diabetes in high- and intermediate-risk populations, respectively.

The NIAID Tetramer Facility, with additional funds from the National Cancer Institute, produces peptide-major histocompatibility complex reagents for T-cell detection and has provided more than 500 tetramers to investigators in its first 18 months of operation. Reagents are provided for the study of T-cell responses relevant to vaccine research and development for many diseases, including intracellular bacterial, viral, and parasite infections and autoimmune diseases. Information on the NIAID Tetramer Facility can be found at http://www.niaid.nih.gov/reposit/tetramer/index.html.

Division of Microbiology and Infectious Diseases

Because vaccines can provide a safe, effective, and efficient means to prevent illness, disability, and death from infectious diseases, research leading to new and improved vaccines is a high priority of DMID. The goal of the DMID Program for the Accelerated Development of Vaccines, established in 1981, is to support research leading to vaccines that will improve the health of the nation. Factors that influence priorities for vaccine research include the morbidity and mortality associated with each infectious disease, critical evaluation by the Institute of Medicine (IOM) of the National Academy of Sciences, assessment of research gaps and opportunities, as well as recommendations made by the National Vaccine Advisory Committee and other advisory groups. DMID designs and implements a comprehensive research program to develop new or improved vaccines that will prevent or reduce the incidence of such infections in susceptible populations. Advances in the fields of microbiology,

immunology, and biotechnology are applied to the development of new vaccines and to the improvement of existing vaccines through research support on the following:

- New vaccines against major diseases caused by respiratory syncytial virus (RSV), malaria, group A and group B streptococci, as well as other bacterial, parasitic, and fungal infections of both children and adults;
- Improved vaccines against diseases such as influenza virus, viral hepatitis, and TB;
- Vaccines to prevent neonatal infections such as group B streptococcus and congenital diseases caused by cytomegalovirus infection, toxoplasmosis, syphilis, gonorrhea, and chlamydial infections;
- New vaccines to prevent and control emerging diseases, including *Helicobacter pylori* and drug-resistant bacteria such as pneumococcus; and
- Novel technologies that are needed to enhance the effectiveness of vaccines, such as adjuvants, proteosomes, and plasmid DNA approaches.

Vaccines of high public health relevance, developed often in collaboration with industry, are tested for safety and efficacy in preclinical studies. If they remain promising, they may be evaluated in the DMID Vaccine Evaluation Network, which includes the VTEUs and other units at universities across the United States. New vaccine candidates continue to be developed, spurred on by advances in the basic sciences. These vaccine units are an integral part of NIAID vaccine research efforts and support carefully planned and designed clinical trials of novel bacterial, parasitic, and viral vaccines and other biologicals in people of all ages and risk categories. Also of importance is the surveillance of pathogens that are of special interest to NIAID, and the capacity to undertake focused research directly linked to vaccine biology and immunology.

In addition, the evaluation of vaccine safety is an integral component of the NIAID vaccine research program. Safety is evaluated in every vaccine clinical trial sponsored by NIAID. Study participants are closely monitored for any adverse effects of the vaccinations they receive. Specific safety issues, such as the use of novel cell substrates for vaccine development and the evaluation of combination vaccines, are explored through scientific consultation with other Federal agencies and in coordination with the National Vaccine Program Office (NVPO).

DMID also supports research on the development and more effective use of approaches to the following:

- Generating long-lasting protective immunity against various infectious agents;
- Favoring the development of mucosal immunity or the production of an antibody of a given isotype;
- Increasing the immunogenicity of candidate vaccines or favoring the expression of a cell-mediated cytotoxic immune response; and
- Simplifying immunization regimens to reduce the number of immunizations required for protection, as well as the number of visits to health care facilities and associated costs.

With an integrated and comprehensive research program in infectious diseases, microbiology, and immunology, NIAID is prepared to lead research efforts on the development of safe and effective vaccines for the prevention of a variety of infectious diseases. Thus, DMID/NIAID is recognized as an effective participant in U.S. national vaccine policy. In the United States, NIAID collaborates with other vaccine agencies, including the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration, on issues of vaccine research, vaccine safety, and national immunization strategies, coordinated through the NVPO.

Internationally, DMID/NIAID participates with other national research agencies in the development and support of programs such as the Global Alliance for Vaccines and Immunization (GAVI) and the Multilateral Initiative on Malaria (MIM). GAVI was established in 1999 as an alliance of global partners to replace the Children's Vaccine Initiative. This global alliance has the support and participation of international agencies (World Health Organization, UNICEF, World Bank), as well as bilaterals, industry, nongovernment agencies, and foundations. The creation of the Global Alliance has been accompanied by significant financial commitments from the Bill and Melinda Gates Children's Vaccine Program. The mission of GAVI is to save children's lives and protect people's health through the widespread use of safe vaccines, in the belief that every child, regardless of place of birth or socioeconomic status, should be protected against vaccine preventable diseases of public health priority.

Priority vaccine initiatives include the 1997 NIAID Research Plan for Malaria Vaccine Development and the 1998 Tuberculosis Vaccine Research Plan. For example, the Malaria Plan represents a collaboration between extramural and intramural divisions at NIAID and, for full implementation, will necessitate international collaborations as well as strategic linkages with industry.

The costs related to infectious diseases are enormous, not only in the United States but worldwide. In the United States, billions of dollars are spent each year in direct medical costs and loss in productivity due to bacterial, viral, and parasitic infections. It has been demonstrated repeatedly that substantial direct and indirect savings result when diseases are controlled or prevented by effective vaccine programs.

The IOM has recently completed a study, *Vaccine Research Priorities for the 21st Century*, which was commissioned by NIAID and other Institutes, and funded with support from 1 percent NIH evaluation funds. As part of the study, a quantitative model for the development of priorities for both infectious and noninfectious vaccine targets (such as cancer and autoimmune diseases) was created, and a reassessment of disease burden for a number of conditions was conducted.

NIAID, in collaboration with the CDC, requested that the IOM establish an independent expert committee to review hypotheses regarding the relationship between specific vaccines and alleged adverse events. In response, the IOM created an Immunization Safety Review Committee in September 2000. For each concern presented, the panel review will assess its plausibility and specify if any additional actions (e.g., research, surveillance) should be undertaken. The panel will meet at least three times per year, and findings will be disseminated to the public.

DMID will continue to apply the latest advances in the fields of immunology, microbiology, and biotechnology to the development of new or improved vaccines against infectious diseases. These applications include the following:

- Use of recombinant DNA technology for the production of defined immunogens, as well as the preparation of plasmid DNA vaccines;
- Development and use of various immunomodulators to augment the immune response to poorly immunogenic candidate vaccines;
- Development of novel vaccine delivery systems to promote long-lasting immunity or to generate immune response in selected host tissues; and
- Research on novel approaches to the development of multicomponent vaccines and simpler vaccination regimens to reduce health care costs and the number of visits to the health care facility.

Division of Intramural Research

DIR conducts a wide-ranging vaccine program. Extensive efforts are under way to develop vaccines to prevent viral diseases of worldwide importance, such as malaria, genital herpes, hepatitis E, dengue fever, AIDS, and diseases caused by respiratory syncytial virus and parainfluenza viruses. A hepatitis A vaccine that was developed in one of the DIR laboratories has been licensed. In addition, vaccines against chlamydial agents that cause sexually transmitted diseases and against the spirochete that causes Lyme disease are under investigation. Candidate vaccines for influenza, parainfluenza, and respiratory syncytial viruses are tested for safety, immunogenicity, genetic stability, and efficacy at the DIR-supported VTEU. Each year about 10 such candidate vaccines are evaluated at this VTEU. DIR also has a substantial program directed at the development of a vaccine for malaria. In addition, research on other parasitic infections, such as schistosomiasis, leishmaniasis, and filariasis, may lead to the development of vaccines. DIR researchers use a full range of state-of-the-art techniques, including recombinant DNA technology.

NIAID Dale and Betty Bumpers Vaccine Research Center

The Vaccine Production Program at the VRC is dedicated to the development of manufacturing processes that will provide material for clinical trials as well as a solid foundation for the eventual manufacture of vaccines. This program will use existing laboratory facilities at the VRC, contract agreements, and construction of a **c**urrent **G**ood **M**anufacturing **P**ractices (cGMP) facility for the development and manufacture of HIV vaccine candidates.

The VRC laboratories, located in Bethesda, Maryland, include cell banking, fermentation, cell culture, purification, and quality-control areas. Process development in these laboratories will focus on the production of adenoviral and DNA-based vaccines. The laboratories will develop techniques for the construction of adenoviral packaging cell lines, the design and optimization of cell-culture systems, the development of effective methods of purification, and strategies for final vaccine formulation. The quality-control labs will

develop appropriate characterization and in-process assays to monitor production quality.

In addition, a cGMP pilot plant is being planned for the production of HIV vaccines for phase I and phase II human trials. This facility, located in Frederick, Maryland, will perform the scale-up and final development of selected manufacturing processes. Quality-control labs, as well as a quality-assurance organization, will also support pilot plant production.

The manufacture of clinical materials has already commenced, with multiple organizations providing materials to the VRC, under NIH contracts, for development and clinical production. These contract mechanisms will help expedite the Vaccine Production Program delivery of novel vaccine candidates for clinical evaluation.

AIDS Vaccine Discovery and Development

Research laboratories within the VRC are in the process of generating multiple gene-based vaccine candidates by inserting HIV cDNAs into relevant plasmid backbones and vectors. Strategies to optimize immunogenicity include modifications of the nucleotide sequence for optimal codon usage and mutagenesis to define alternative proteins with enhanced immunogenicity.

In August 2000, the VRC sponsored a 2-day meeting on the structure of the HIV-1 glycoprotein that brought together structural biologists studying the physical structure of HIV gp160 with virologists and immunologists focused on AIDS vaccine research. The meeting highlighted key areas of focus for the structure-based rational design of HIV vaccines, which will be studied by VRC investigators with expertise in x-ray crystallography and gp160/viral envelope structure.

Vaccine Discovery and Development—Other Infectious Diseases

The Ebola virus is one of a group of viruses that causes hemorrhagic fever in monkeys and humans. It is an extraordinarily virulent pathogen that kills up to 90 percent of infected individuals, most often by causing massive internal bleeding. As is the case for HIV, no vaccine against Ebola exists, nor is there any effective cure for infected individuals.

VRC investigators discovered that, when broken down inside an endothelial cell, a glycoprotein specific to Ebola causes cell death. Moreover, they isolated the major Ebola virus gene that codes for the protein portion of the glycoprotein molecule and identified the section of that gene that is responsible for the protein's ability to combine with a carbohydrate to produce a glycoprotein. Glycoproteins form part of the outer covering, or envelope, of a viral particle (virion). The glycoprotein identified by the investigators enables Ebola virions to attach to vascular endothelial cells and facilitates the insertion of Ebola virus genetic material into these cells. Identifying the gene and gene product responsible for vascular endothelial cell death may facilitate the development of effective medications to treat Ebola as well as the development of a vaccine that will prevent the cellular processes leading to the massive hemorrhaging characteristic of this disease.

Drug Research and Development

The development of therapies to treat infectious and immune-mediated diseases is a key component of NIAID's mission. Basic research serves as the foundation for drug development through scientific advances in microbiology and immunology. Advances in these areas help to identify potential targets for therapeutic agents and potential strategies for treating infectious and immune-mediated diseases. Through collaborations with industry, academia, and other Government agencies, NIAID has established research programs to facilitate drug development, including databases to screen chemicals for their potential use as therapeutic agents, facilities to conduct preclinical screening of promising drugs, and clinical trials networks to evaluate the safety and efficacy of drugs and therapeutic strategies.

Division of Acquired Immunodeficiency Syndrome

The Division of Acquired Immunodeficiency Syndrome (DAIDS) devotes substantial resources to the discovery and development of new therapeutics, attempting to focus resources on areas of promise that receive insufficient support elsewhere. A strong portfolio of basic research serves as the foundation for these activities.

Over the past 11 years, researchers have concentrated their drug-discovery efforts on a relatively small number of viral targets: reverse transcriptase (RT), the enzyme that catalyzes the synthesis of viral DNA from the RNA template present in the incoming, or infecting, virion, and protease (PR), the enzyme that effects HIV maturation by cleaving and processing viral precursor proteins to their mature form. There has been a great deal of success in suppressing HIV and decreasing the incidence of opportunistic infections by combining treatment with several RT and PR inhibitors (known as highly active antiretroviral therapy or HAART). Nonetheless, many problems have emerged with these regimens, including the development of drug resistance, metabolic abnormalities and toxicities, and noncompliance due to the complexity of these regimens. Moreover, damage to the immune system is only partially repaired by HAART. Thus, there continues to be an urgent need for new therapeutic entities and approaches to expand the number and clinical benefit of currently approved therapies.

HIV therapeutics are discovered through a number of approaches beginning with basic research on the structure and function of viral and cellular proteins critical to the virus life cycle, and immunopathogenic studies to further understand the nature of HIV-mediated immune deficiency, and strategies to restore or reconstitute effective immune function. DAIDS supports basic and applied research in pathogenesis, virology, immunology, and structural biology as it relates to HIV. This is the foundation for targeted drug discovery, pursued through investigator-initiated grants, Small Business Innovation Research (SBIR) grants, contracts, the Novel HIV Therapy: Integrated Preclinical/Clinical Development Program (IPCP), and the HIV Therapeutics: Targeting Research Gaps Program.

The IPCP supports the discovery, preclinical evaluation, development, and pilot clinical study of novel agents and strategies to suppress HIV replication, interfere with disease progression, reconstitute or repair

immune damage, genetically protect cells against HIV, and ameliorate the consequences of infection. Once a novel therapeutic is discovered, development proceeds through additional *in vitro* testing. Additional information is obtained by evaluating the agent's activity against a range of HIV isolates, testing in animal models of HIV infection, when appropriate, assessing the toxicity in different cell lines and animal models, and conducting pharmacological studies. If appropriate, the IPCP supports early clinical evaluation in human studies.

The Targeting Research Gaps Program focuses on the development of new delivery or formulation methods to enhance the clinical potential of anti-HIV drugs. It also supports research designed to validate new viral and cellular targets for inhibiting HIV and for developing new drugs, and seeks to improve our understanding of the role of innate immune responses in susceptibility to HIV infection and modulation of disease progression, as well as their potential use in therapeutics.

Another important element of the DAIDS therapeutics discovery and development effort is the acquisition and dissemination of information on agents or strategies that show potential for treating HIV infection and associated opportunistic pathogens. These activities include assisting drug sponsors in obtaining additional *in vitro* and *in vivo* activity data. DAIDS also conducts a program of surveillance by developing, maintaining, and using databases of chemicals with known or potential activity against HIV and associated opportunistic pathogens. DAIDS scientific staff use these databases to monitor compounds already under investigation and to identify additional entities to be pursued. Information from the databases is available to the scientific community upon request.

Once a therapy has been developed, DAIDS conducts clinical trials to examine its effectiveness in improving the quality and duration of life for HIV-infected individuals. The trials are conducted through one of three large multicenter clinical trials networks—the Adult AIDS Clinical Trials Group (AACTG), the Pediatric AIDS Clinical Trials Group (PACTG), and the Terry Beirn Community Programs for Clinical Research on AIDS (CPCRA). These programs investigate therapeutic agents and novel treatment approaches, including studies to evaluate safety, dose, activity, efficacy, and optimal use. Together, they represent the largest AIDS clinical trials network in the United States and probably in the world.

Division of Allergy, Immunology and Transplantation

Research and development of drugs and biologics to treat and prevent immune-mediated diseases are within the purview of the Division of Allergy, Immunology and Transplantation (DAIT). Areas of research include therapeutic approaches to autoimmune diseases, primary immunodeficiencies, asthma and allergic diseases, and rejection of transplanted organs, cells, and tissues, including bone marrow. One example of DAIT's commitment to this work is the establishment of collaborative research groups to study the molecular and immunologic mechanisms that underlie the effects of immunotherapeutic agents currently being evaluated in clinical trials. In addition, the use of molecular methods for transferring genes

encoding immunotherapeutic molecules into lymphocytes or mucosal membranes for delivery to the patient is being investigated. This method has the potential for augmenting host defenses or altering immune responses.

Several investigations are under way to evaluate new and potentially more effective therapies for asthma and allergic diseases. New therapeutic interventions include multiple approaches to immunization and development of new agonist or antagonist medications. The Division's Autoimmunity Centers of Excellence are performing pilot clinical trials for several new immunomodulatory approaches to prevent and treat autoimmune diseases. These Centers encompass expertise in various autoimmune diseases, including multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel diseases, and type 1 diabetes.

DAIT's Cooperative Clinical Trials in Adult and Pediatric Kidney Transplantation are evaluating a variety of therapies to improve graft survival and to prevent acute and chronic graft rejection. New approaches and therapeutic agents under investigation include monoclonal antibodies in conjunction with standard immunosuppressive therapy, new immunosuppressive drugs to prevent and reverse chronic rejection, pretransplant induction therapies to decrease acute graft rejection and to prevent the onset of chronic rejection, and intravenous gamma globulin to reduce high levels of sensitization among some end-stage renal disease patients, thereby enabling them to become candidates for transplantation.

DAIT, with cosponsorship from the National Institute of Diabetes and Digestive and Kidney Diseases and the Juvenile Diabetes Research Foundation International, continues to support the Immune Tolerance Network (ITN) established in FY 1999. This unique international multi-institutional consortium brings together more than 70 researchers and clinical specialists from 40 institutions in nine countries. The ITN works closely with academic investigators and industry to investigate new approaches to inducing donor-specific immune tolerance. Network investigators are conducting clinical trials to test the ability of "tolerogenic" approaches to support long-term survival of transplanted kidneys and human islet cells to treat type 1 diabetes. Tolerogenic therapies disable only the immune cells that attack transplanted organs, letting other immune cells function normally to protect the body from infectious agents and cancer cells. In addition, the ITN will also conduct clinical trials of new tolerance-inducing therapies in autoimmune diseases, such as systemic lupus erythematosus, rheumatoid arthritis, and multiple sclerosis, as well as allergic diseases and asthma.

Division of Microbiology and Infectious Diseases

The Division of Microbiology and Infectious Diseases (DMID) supports research to facilitate the discovery and evaluation of new drugs for infectious diseases. This research is supported at all three phases of the process: discovery, preclinical evaluation, and clinical evaluation. Current drug-development efforts address a wide spectrum of infectious agents, including hepatitis, tuberculosis, sexually transmitted diseases (STDs), malaria, fungal diseases, and pneumonia.

The drug research and development efforts of DMID reflect the Division's broad purview and accordingly encompass a diverse range of target organisms and treatment strategies. The activities support all stages of drug discovery and development, from the test tube to the bedside and, especially for animal model and clinical research, involve close collaborations with colleagues from the pharmaceutical industry and the Food and Drug Administration (FDA).

DMID also supports more than 30 large-scale genome-sequencing projects; this information has the potential for further advancing the discovery and evaluation of new therapeutic agents for infectious diseases.

Discovery and Preclinical Evaluation

DMID maintains an active antiviral screening program that tests potential antiviral agents *in vitro* for activity against hepatitis B virus (HBV), influenza, respiratory syncytial virus (RSV), cytomegalovirus (CMV), West Nile virus, vaccinia, and other herpes and respiratory viruses. DMID also collaborates with the U.S. Army Medical Research Institute on Infectious Diseases antiviral program in the search for therapies for exotic viruses such as Ebola and Sin Nombre. DMID and DAIDS staff members also interact closely on drug-discovery research and therapeutic evaluation efforts.

DMID supports investigators conducting basic and applied research on the discovery and design of antiviral agents. These projects have led to the design of new drugs for influenza, CMV, and hepatitis infections. Preclinical evaluations of antiviral therapies are also conducted in animal models of human viral infections. Recent studies have included the demonstration of the superiority of the combination of acyclovir and the herpes simplex virus-specific antibody over either agent alone as a therapy for the mouse equivalent of neonatal herpes, and the demonstration that an orally available anti-influenza compound in mice infected with influenza was as good or better than a previously identified, chemically similar compound, which cannot be taken by mouth. Other recent findings have identified several drugs with activity against members of the poxvirus family, which might be helpful in the event of a bioterrorist attack using smallpox.

Basic research on microbe replication has led to the identification of new therapeutic targets for viruses, bacteria, and parasites and of strategies to develop new agents based on this knowledge. For example, research projects on malaria include identification and characterization of unique parasite biochemical pathways that may serve as targets for drugs; determination of mode of action of existing and potential drugs; and analysis of the mechanisms by which the parasite has become resistant to existing drugs.

An increasingly important contributor to the emergence of many infectious diseases, including pneumonia and tuberculosis, is the emergence of drug-resistant pathogens. Microbes that were once easily controlled by antimicrobial drugs are causing infections that no longer respond to treatment with these drugs. This is becoming an increasingly important public health concern. In response, the Public Health Service, under the leadership of the NIH, FDA, and the Centers for Disease Control and Prevention, has developed an Antimicrobial Resistance Action Plan, which

provides a blueprint for specific, coordinated Federal actions to address the emerging threat of antimicrobial resistance. There are four areas of emphasis: (1) surveillance, (2) prevention and control, (3) research, and (4) production development; NIAID has the lead in the area of research.

Clinical Studies

DMID clinical research is either supported by individual grants or by contract-supported programs, such as the Collaborative Antiviral Study Group (CASG) and the Mycoses Study Group (MSG). The CASG is supported by a single award to the University of Alabama at Birmingham and by subcontracts to more than 100 collaborating sites. The CASG is currently evaluating new therapies for neonatal herpes, congenital CMV, herpes simplex encephalitis, influenza, and RSV infections. Studies of experimental combination therapies for HBV and HCV are in the planning stages. Recent treatment advances have included the demonstration by the CASG that acyclovir combined with prednisone was more effective than either agent alone in improving quality-of-life end points for people with shingles. These end points include the amount of time until a patient could sleep through the night and the amount of time until return to work. In addition, the CASG has demonstrated that an anti-CMV drug can decrease hearing loss in infants with symptomatic congenital ear infection.

The NIAID MSG, funded by both DMID and DAIDS, supports clinical trials examining antifungal therapy in the opportunistic and endemic mycoses. In early 2001, in conjunction with the scheduled completion of the MSG contract, two new contracts are expected to be awarded to comprise the Bacteriology and Mycology Study Group (BAMSG) and the Bacteriology and Mycology Biostatistical Unit (BAMBU). This change expands the scope of work to include a new patient risk group to address resistance to antibacterial agents in a nosocomial setting and to provide for a separate biostatistical and operations unit.

Two studies recently implemented by the MSG are a comparison of chronic suppressive therapy versus episodic therapy with fluconazole in HIV seropositive patients with recurrent thrush (phase IV) and a pharmacokinetic study of itraconazole in a cyclodextrin solution in bone marrow transplant recipients. Other DMID-supported research groups that conduct drug evaluations as a part of their overall mission include the Vaccine and Treatment Evaluation Units, the International Centers for Infectious Diseases Research, and the Sexually Transmitted Diseases Cooperative Research Centers. In 2000, NIAID launched a phase III Efficacy Trial, Azithromycin versus Benzathine Penicillin for the Treatment of Early Syphilis, through its STD Research Centers program. The purpose of this study is to determine if azithromycin, a drug approved for treatment of other infections, is as effective for syphilis therapy as the usual penicillin treatment. In addition, single-project grants and contracts also support therapeutic evaluations for a number of diseases.

Treatment-Related Research

The first step toward appropriate treatment of an infectious disease is the availability of a sensitive and specific diagnostic reagent. DMID supports numerous efforts aimed at

developing more effective diagnostic tools for infectious diseases. For example, DMID supports the development and manufacture of rapid, inexpensive diagnostic tests for STDs. The Division also supports research focused on the development of topical microbicides, which are bactericidal or virucidal intravaginal preparations that would be used by women to prevent sexually transmitted infections.

On September 26 and 27, 2000, NIAID convened the *Summit on Development of Infectious Disease Therapeutics*, a meeting with industry to discuss the state of development of new therapeutics for infectious diseases. The purpose of this meeting was to discuss the role and nature of NIAID/pharmaceutical collaborations in antimicrobial drug development for public health needs and to learn how NIAID could better assist industry and academia in these endeavors. NIAID plans to develop a research initiative in 2001 to address the recommendations stemming from this meeting.

Division of Intramural Research

NIAID intramural researchers are studying many different new therapies for diseases as varied as AIDS, malaria, and tuberculosis. Some of the most promising work involves the use of gene therapy to treat diseases that are caused by simple gene mutations. Chronic granulomatous disease (CGD) is a primary immune deficiency caused by a defect in an enzyme called phagocyte NADPH oxidase, or phox. Mutations in one of four different genes can cause this defect, which leads to frequent and often life-threatening infections of the skin, lungs, and bones with localized, swollen collections of inflamed tissue called granulomas.

NIAID's Division of Intramural Research (DIR) investigators identified and cloned the phox genes that are affected in two genetic forms of CGD, developed retrovirus vectors encoding each of the four CGD genes, and demonstrated that these vectors can achieve functional correction of CGD in the test tube. Next, in a phase I clinical trial, DIR investigators removed stem cells from five people with CGD. The researchers inserted the correct form of the phox gene into the stem cells and then transfused the corrected cells back into each patient. Samples of the patients' blood later demonstrated the appearance of small numbers (1 in 5,000) of oxidase normal gene-corrected neutrophils in the peripheral blood of these patients for 2 to 6 months.

Although the numbers of gene-corrected cells were small, the study demonstrates unequivocally that gene therapy of stem cells can produce functionally normal blood cells in patients for a prolonged period. This finding could have important clinical implications for the treatment of CGD. Because life-threatening infections caused by CGD may require many weeks or months of therapy and relapses are frequent, use of gene therapy to provide even short- to medium-term production of phox-positive cells may be clinically beneficial. Future studies will include further clinical trials of gene therapy for CGD targeting both the most common X-linked form of CGD, as well as the autosomal recessive forms of this disease.

Topical Microbicides

Worldwide, women face the greatest risk of acquiring HIV and other sexually transmitted diseases (STDs) due to substantial mucosal exposure to seminal fluids, the prevalence of non-consensual sex, sex without condom use, and hidden, high-risk behaviors of their partners. Despite the overwhelming risks presented to them, women have few available means for protecting themselves against HIV and other STDs. The development of chemical barriers, known as topical microbicides, that can be used intravaginally or intrarectally to inactivate HIV and other STD agents is being explored to provide a safe, effective, and easy means of protection. To increase their use and acceptability, topical microbicides should be invisible, safe, non-irritating, and inexpensive, as well as fast-acting, easy to store, and effective when used at least once or twice a day.

In addition, it will be important for topical microbicides to be available in both spermicidal and non-spermicidal formulations so that women do not have to put themselves at risk for acquiring HIV and other STDs to conceive a child. An individual's contraceptive choices may change over a lifetime. Non-contraceptive microbicides would be extremely useful, for example, to women who use one of the many safe, effective methods for contraception that either have no protective effect against STDs or may exacerbate the risk of STD infection. Either way, individuals will want protection from sexually transmitted infections if they are sexually active.

NIAID has been encouraging the development of topical microbicides through basic research, preclinical product development, and clinical evaluation. The Institute supports six topical microbicide program project grants that focus on basic research and preclinical product development. NIAID also supports large-scale screening of potential HIV transmission-blocking agents. Over the past year, more than 1,700 compounds have been obtained from private-sector, academic, and governmental sources and tested *in vitro* for their ability to block HIV transmission from infected T cells to cultures of human cervical cells. More than 30 compounds with minimal toxicity have been identified that can effectively block HIV transmission. Assays have also been developed to evaluate the effectiveness of these compounds under various physiologic conditions to mimic the vaginal physiology, such as in the presence of mucins that stimulate the vaginal mucosal environment. Researchers are also determining whether potential HIV transmission-blocking agents cause intravaginal irritation or other adverse effects in experimental animals and whether compounds remain stable in the vagina after delivery.

A number of animal models currently exist for testing microbicides, including nude mice for human papillomavirus (HPV) infection, macaques for SIV/SHIV (SIV or simian immunodeficiency virus is an HIV-like virus that infects nonhuman primates; SHIV is a genetically engineered hybrid virus that has an HIV envelope and an SIV core) and for chlamydia, and guinea pigs and mice for genital herpes.

Research continues to evaluate and confirm the use of animal models for studying topical microbicides, and recently, NIAID-funded researchers established a reproducible nonhuman primate model for studying the safety and effectiveness of a topical

microbicide for the prevention of chlamydial infection. This research found that the anatomy and vaginal flora of pig-tail macaque monkeys and humans are remarkably similar.

Several promising topical microbicide candidates are in various stages of testing. BufferGel, a nondetergent microbicide that inactivates pathogens such as HIV in the laboratory, was recently found to be safe and acceptable in human trials. The trial was conducted in two parts, first in the United States, which showed that it was nontoxic and well tolerated. An expanded phase I study was then conducted to examine the safety, acceptability, and use of BufferGel in relevant populations in India, Thailand, Zimbabwe, and Malawi. Although some women in this study reported minor side effects, the overall tolerance of BufferGel was high. Plans are under way to begin a phase III efficacy trial of BufferGel in 2001. Data from a domestic and international phase I study of another topical microbicide, Pro2000, are currently being analyzed. Another study designed to assess the safety, acceptability, and preliminary effectiveness of a carageenan-based microbicide, which blocks adherence of HIV to host cells, was initiated at several sites in South Africa in collaboration with the Population Council.

A particularly novel approach to microbicides involves the use of a bacterial strain, called *Lactobacillus crispatus*, which naturally colonizes the vagina of many women. These bacteria produce hydrogen peroxide, a chemical that kills harmful microbes, including those that cause STDs. Research has shown that women infected with *L. crispatus* have less risk of getting gonorrhea, HIV infection, and bacterial vaginosis, a type of vaginal inflammation. NIAID-funded researchers are also conducting a trial in which lactobacilli-containing suppositories are inserted into the vagina of young women with histories of STDs.

Plants offer another potential method for producing protective antibodies at low cost and in large enough quantities that can be used worldwide as a topical microbicide. Recently, NIAID-sponsored research demonstrated the effective use of rice-produced antibodies in neutralizing viruses that cause oral and genital herpes as well as HPV, the cause of genital warts and cervical cancer. NIAID-funded researchers now plan to develop a topical gel that contains anti-herpes simplex virus (HSV) antibodies for use in protecting against genital herpes.

Monoclonal antibodies have also been shown to provide complete protection against genital herpes in the mouse model, leading NIAID-funded researchers to conduct pilot studies in humans. These studies demonstrated that a single application of antibodies delivered to the human vagina may remain there long enough to provide protection for more than 1 day.

Asthma and Allergic Diseases

Allergic diseases, including asthma, are among the major causes of illness and disability in the United States. For example, more than 50 million Americans, one out of every five, are reactive to at least one of eight selected allergens known to contribute to allergic illness.[10] Allergic rhinitis affects an estimated 13 percent of the U.S. population, or 36 million Americans.[11] The number of individuals with allergic rhinitis has increased by 25 percent from 1979-1981 to 1990-1992.[12]

Atopic dermatitis, one of the most prevalent skin diseases, is common in infants and children. The prevalence among children is estimated between 3 and 10 percent. The incidence appears to be increasing among children born in the late 1970s, compared to those born in the 1960s.[13] Contact dermatitis and other eczemas account for approximately 7 million physician office visits per year.[14]

Food allergy is estimated to occur in approximately 8 percent of children ages 6 years and under, and in approximately 1 percent of adults.[15] The prevalence of allergy to peanuts and tree nuts is approximately 1 percent, and allergy to these two foods is among the leading causes of fatal and near-fatal food-allergic reactions.[16, 17] Food allergy is the most frequent single cause of emergency room visits for anaphylaxis and accounts for 33 percent of such emergency room visits.[18, 19]

In 1998, there were an estimated 17 million persons (6.4 percent) in the United States who had asthma.[20] Asthma was the first-listed diagnosis for more than 451,000 hospitalizations, 169,000 of which were for children under 15 years of age. The average hospital stay for asthma was 4 days.[21, 22] Asthma is more prevalent among African Americans (5.8 percent) than whites (5.1 percent), and the highest prevalence is among ages 5 to 14 (7.4 percent).[23, 24] Asthma is also more prevalent among African-American children who are 6 to 11 years old than among white children of the same age (9.4 percent and 6.2 percent, respectively).[25] For U.S. children ages 5 to 14, asthma prevalence increased from 4.3 percent in 1980 to 7.4 percent in 1993-1994.[26]

The cause, pathogenesis, diagnosis, treatment, and prevention of asthma and allergic diseases represent major areas of emphasis for NIAID's Division of Allergy, Immunology and Transplantation (DAIT). NIAID vigorously pursues research on asthma and allergic diseases by fostering investigator-initiated projects and by supporting a national network of research centers, cooperative clinical studies, and demonstration and education research projects.

In the ongoing Inner-City Asthma Study (1996-2001), NIAID and the National Institute of Environmental Health Sciences are supporting a comprehensive environmental intervention to reduce exposure to major indoor allergens. In this 950-patient study, the baseline data show unanticipated and very high rates of sensitization to a range of indoor allergens. Preliminary data highlight many serious obstacles to allergen remediation in inner-city environments.

NIAID, through DAIT, supports 12 Asthma and Allergic Diseases Research Centers to conduct basic and clinical research on the immune mechanisms, treatment, and prevention of asthma and allergic diseases. Specific program goals are to advance understanding of the etiology and pathogenetic

mechanisms of allergic and immunologic diseases, and to apply this expanded knowledge base to the development of improved methods to diagnose, treat, and prevent a wide variety of disorders. In addition to concentrating on traditional basic and clinical research, some of these centers conduct demonstration and education research projects to test the effectiveness of interventions to promote health or prevent disease in defined populations.

In FY 2000, NIAID, along with other Institutes and Agencies of the Department of Health and Human Services (DHHS), published a document titled *Action Against Asthma*, which defines plans for coordinating DHHS efforts in asthma surveillance, research, and public health practice (http://aspe.hhs.gov/sp/asthma). In addition, NIAID collaborated with the American Academy of Allergy, Asthma and Immunology and other professional allergy organizations on a task force to develop clinical practice guidelines for allergic diseases and asthma titled *The Allergy Repor*t, which was published in 2000 (http://www.theallergyreport.org). NIAID also contributed to the chapter on respiratory diseases for the Healthy People 2010 initiative, led by the DHHS Office of Disease Prevention and Health Promotion. This initiative defined goals for increasing life expectancy and quality of life of patients with asthma, as well as eliminating racial and ethnic disparities.

Scientific advances over the past several decades have revolutionized our understanding of the human immune system and have contributed significantly to extraordinary improvements in the treatment of many immune-mediated diseases. As the primary NIH Institute for research in immunology, NIAID has been at the forefront of many of these advances, including discoveries leading to the characterization of asthma and allergic diseases as immunological disorders. With an enhanced understanding of the role of immune dysfunction in the pathogenesis of asthma and allergic diseases, NIAID is uniquely positioned to apply fundamental knowledge to develop novel therapies and eventually to prevent disease onset.

An important NIAID intramural study currently under way is focusing on interleukin-4 (IL-4), a central regulator of allergic inflammatory responses, in the generation of inflammation in asthma. IL-4 controls polarization of naive CD4 T cells to the Th2 phenotype. Appropriate Th2 responses are part of the protective arsenal of the immune system; however, an over-exuberant Th2 response can lead to allergic diseases. Intramural scientists are conducting a phase II study examining the efficacy of a soluble IL-4 receptor, which blocks IL-4 from interaction with its cellular receptor, in the treatment of asthma. These results should contribute to understanding how allergen-specific Th2 responses are maintained and to understanding the mechanism of action of soluble IL-4 receptor therapy.

Autoimmune Diseases

Autoimmune diseases, which result from a disordered attack of the immune system on the body's own tissues, affect more than 5 percent of the U.S. population and disproportionately afflict women. These diseases are a significant cause of chronic morbidity, costing billions of dollars annually in health care expenses and lost productivity. Autoimmune disorders can be divided into two main groups: organ-specific and non-organ-specific diseases. Organ-specific diseases are characterized by immune reactions and tissue damage localized to a single organ or tissue. For example, in type 1 diabetes and multiple sclerosis, the primary lesions are localized in the pancreas and the central nervous system, respectively. In contrast, non-organ-specific diseases, such as systemic lupus erythematosus (SLE), are characterized by immune reactivity against antigens distributed throughout the body, resulting in widespread damage.

NIAID's Division of Allergy, Immunology and Transplantation (DAIT) supports a broad range of basic and clinical research programs in autoimmunity. Basic research focuses on understanding the genetics of autoimmunity, elucidating the mechanisms that underlie self-tolerance, developing approaches to induce self-tolerance, and characterizing pathways of immune-mediated tissue destruction. Knowledge gained from basic studies provides the rationale for developing clinical tests to diagnose autoimmune diseases and novel treatments for ongoing disease. DAIT cooperates with many organizations, including other NIH Institutes and private organizations, in supporting research in autoimmune diseases. In addition, NIAID chairs the National Institutes of Health (NIH) Autoimmune Diseases Coordinating Committee, established in FY 1998 at the request of Congress to increase collaboration among the many NIH Institutes, private groups, and other Federal agencies interested in these diseases and to facilitate the development of coordinated research plans. The first report of the Autoimmune Diseases Coordinating Committee, published in December 2000, provides further details on the individual initiatives, sponsors, and current and planned research on autoimmune diseases. The report is located at http://www.niaid.nih.gov/dait/pdf/adcc_rev.pdf.

In FY 2000, NIAID continued several programs established in FY 1999 with additional appropriations for autoimmune disease research. These include the Autoimmunity Centers of Excellence (ACE), New Imaging Technologies for Autoimmune Disease, the Human Immunology Centers of Excellence, and the autoimmunity component to the Immune Tolerance Network (ITN).

DAIT supports a large program of investigator-initiated projects in autoimmune disease research, as well as clinical trials, basic and clinical resources, and several ongoing initiatives. Under the ACE, two clinical trials were initiated in FY 2000. The first clinical trial will test the safety and efficacy of anti-CD20 in SLE. The second will examine the effect of anti-C5, a component of the complement system in treating the kidney disease of lupus, and several trials in multiple sclerosis and type 1 diabetes are in development. In addition, several collaborations among ACE investigators will address the immune mechanisms underlying the agents used in these trials. The ITN will perform clinical trials of promising tolerogenic approaches to prevent or treat multiple autoimmune diseases.

An important new area of disease prevention focuses on the use of vaccination approaches to prevent autoimmune diseases. Although no vaccine for any autoimmune disease currently exists, this appears to be feasible based on studies in animal models. Vaccines for autoimmune diseases will be distinct from the vaccines given to prevent infectious diseases. Vaccines for autoimmune diseases will "turn off" a destructive immune response that is directed at the body's own tissues.

In FY 2000, NIAID established the Cooperative Study Group for Autoimmune Disease Prevention, a collaborative network of investigators focused on the development of interventions to prevent autoimmune diseases. This research initiative requires that at least one project focus on type 1 diabetes. Candidate interventions against type 1 diabetes, including vaccines, will be tested in pilot studies and later through larger NIH-supported trial networks. Cosponsors of this research initiative include the National Institute on Diabetes and Digestive and Kidney Diseases (NIDDK), the National Institute of Child Health and Human Development (NICHD), the National Institute of Dental and Craniofacial Research (NIDCR), the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), the NIH Office of Research on Women's Health (ORWH), and the Juvenile Diabetes Research Foundation International (JDRF). Awards are planned for FY 2001.

DAIT, in collaboration with NIDDK and NICHD, supports a multicenter clinical trial, the Diabetes Prevention Trial-1, to test whether insulin administration can prevent or delay the onset of type 1 diabetes in at-risk individuals. The network supporting this trial is being expanded and renewed in FY 2001 through the Diabetes TrialNet Operations Center and Clinical Centers program. In addition, DAIT, in collaboration with NIDDK and JDRF, supports two Diabetes Centers of Excellence to stimulate multidisciplinary research in diabetes, including basic and clinical approaches.

Through the Clinical Trials Network for Stem Cell Transplantation for Autoimmune Diseases, NIAID is sponsoring clinical trials to assess the efficacy of hematopoietic stem cell transplantation for treating severe autoimmune diseases. Mechanistic studies will be performed along with the clinical trials.

Through the Innovative Research in Human Mucosal Immunity initiative, 18 novel exploratory projects were awarded that cover a spectrum of investigations designed to advance our understanding of chronic mucosal inflammation and the role of the mucosal immune system in the induction of tolerance or immunity. NIAID, NIDCR, and the Crohn's and Colitis Foundation of America cosponsor these innovative studies.

DAIT supports two genetics research resources. The Multiple Autoimmune Disease Genetics Consortium collects clinical data and genetic material from families in which at least three individuals are afflicted by two or more autoimmune diseases. The data and samples will be made available to researchers studying the genetics of susceptibility or resistance to autoimmune diseases. The North American Rheumatoid Arthritis Consortium collects clinical data and genetic material from families with rheumatoid arthritis, which are made available to investigators to facilitate the

characterization of the genes underlying susceptibility to rheumatoid arthritis.

In FY 2000, NIAID joined several NIH Institutes and Centers (ICs) and JDRF in supporting the 13th International Histocompatibility Working Group (IHWG), a network of more than 200 laboratories in more than 70 countries that will collect and share data on genes of the human leukocyte antigen (HLA) complex. The IHWG will study five diseases for which the HLA associations have been well characterized, including type 1 diabetes, rheumatoid arthritis, celiac disease, narcolepsy, and spondyloarthropathy. In addition, the IHWG will launch a project to discover single nucleotide polymorphisms (SNPs) in type 1 diabetes-related genes. SNPs are naturally occurring genetic variations that may affect the amount or function of the gene product. Once SNPs are identified, researchers in type 1 diabetes will be able to analyze their patient populations for the presence of these variations. The SNPs will be available in a public database to facilitate the search for susceptibility genes in subjects with type 1 diabetes. The results of these projects will provide a much greater insight into the mechanisms of autoimmune diseases and increase our ability to predict an individual's disease predisposition.

Although we have gained considerable understanding of the immune mechanisms that mediate tissue injury in autoimmune diseases, much remains to be learned concerning the etiologic agents that initiate autoimmune diseases, their genetic susceptibility, the regulation of T-cell and autoantibody production, and the characterization of the cells and chemical mediators of inflammation. NIAID is committed to enhancing our understanding of autoimmune diseases and to developing effective therapeutic approaches and prevention strategies.

Immune Tolerance

The successful induction of immune tolerance is a major therapeutic goal for the treatment of many immune-mediated disorders, including autoimmune diseases such as rheumatoid arthritis, type 1 diabetes, and multiple sclerosis; asthma and allergic diseases; and rejection of transplanted solid organs, tissues, and cells. Tolerance-induction approaches seek to selectively block or prevent deleterious immune responses. For example, in transplantation, donor-specific immune tolerance—a selective blockade of immune responses directed against the graft—would enable long-term graft survival without the complications and risks of global immunosuppressive therapy (e.g., infection, malignancy, and atherosclerosis). In asthma and allergic diseases, the goals of tolerance research are to develop methods to block immune responses, especially allergic (IgE) responses, to those allergens, such as cockroach and house dust mite, that cause or exacerbate these diseases. In autoimmune diseases, tolerance-induction approaches seek to block those immune responses that cause the body to mistakenly attack its own organs, tissues, or cells. Two decades of highly intensive and productive basic research in immunology have provided a solid foundation of knowledge and understanding that will enable the application of promising tolerance-induction strategies to the treatment of human disease.

The NIAID's Division of Allergy, Immunology and Transplantation (DAIT) supports basic research to elucidate mechanisms responsible for immune tolerance, translational research to facilitate the application of immune tolerance to human diseases, and clinical research of novel therapeutic approaches to induce and maintain immune tolerance in humans. New approaches are being sought to achieve the following:

- Improve understanding of the molecular mechanisms responsible for induction and maintenance of immune tolerance;
- Replace or improve currently suboptimal treatment protocols for immune-mediated diseases, such as the use of globally immunosuppressive drugs in transplantation;
- Discover methods to prevent or reverse immune-mediated human disorders for which no effective therapy is currently available;
- Create an efficient research infrastructure for the development and rapid testing of tolerogenic agents in human immune-mediated diseases; and
- Elucidate mechanisms by which tolerogenic agents suppress disease.

In FY 1999, NIAID established the Immune Tolerance Network (ITN), an international consortium of more than 70 basic scientists and clinical investigators, to test promising tolerogenic treatment regimens in four clinical areas: islet transplantation, kidney transplantation, autoimmune diseases, and asthma and allergic diseases. In FY 2000, the ITN received more than 90 proposals for clinical trials, 23 of which were approved for immediate implementation in all four disease areas.

The first clinical trial being conducted by the ITN is the "Edmonton Protocol," an experimental islet transplantation protocol for

brittle type 1 diabetics. (More information on the "Edmonton Protocol" follows in the Transplantation section on page 92.) More information on the ITN is available on the web site http://www.immunetolerance.org.

As clinical therapies for inducing tolerance are advanced, it becomes essential that procedures are developed that can monitor patient progress and provide physicians with timely, accurate, and "predictive" information on the ability of the treatment to control the disease through the development of a tolerant state. These mechanistic assays are termed "tolerance assays." The ITN has established a set of core assay laboratories to develop diagnostic assays for the induction, maintenance, and loss of tolerance. These core facilities include microarray analyses of gene expression, bioinformatics to develop appropriate analytic tools for clinical and scientific data sets developed from the ITN-sponsored clinical trials, ELISPOT analyses of protein expression, and cellular assays for T-cell reactivity. One study is analyzing the immune system of liver transplant recipients who voluntarily stopped taking immunosuppressive drugs and have maintained their transplanted livers for many years. The study focuses on understanding the immune mechanisms responsible for long-term, immunosuppressive-free graft survival and determining whether these patients have developed true immune tolerance to their transplanted livers.

NIAID has a long history of supporting the basic science of tolerance induction, including studies of basic mechanisms of anergy, peripheral tolerance, and central tolerance, such as clonal deletion. These efforts have yielded outstanding progress, and NIAID has now begun to support research to apply the results of these studies in preclinical and clinical transplantation settings. In 1998, NIAID established the Non-Human Primate Transplantation Tolerance Cooperative Study Group to facilitate the application of promising approaches to achieve tolerance in large-animal models of kidney and islet transplantation.

Other DAIT-supported research programs on immune tolerance include the Autoimmunity Centers of Excellence, the NIAID Tetramer Facility, the Human Immunology Centers of Excellence, innovative grants on immune tolerance, and program projects in basic biology, basic immunology, and transplantation tolerance.

Transplantation

Illnesses such as kidney failure, diabetes, leukemia, coronary heart disease, and liver disease affect millions of Americans. For many of these patients, transplantation of solid organs, tissues, or cells can avert and, in some cases, reverse the severe outcomes of these diseases. Transplantation procedures have increased 74 percent from 1988 to 1999,[27] providing relief to tens of thousands of patients. Advances in transplantation have also increased the likelihood of graft acceptance by the recipient's immune system. Today, transplantation procedures are performed using more than 25 different organs and tissues, with first-year graft survival rates often exceeding 80 percent. Despite these successes, two major impediments remain: immune-mediated graft rejection and the critical shortage of donor organs.

Immune-Mediated Graft Rejection

NIAID's Division of Allergy, Immunology and Transplantation (DAIT) supports a broad spectrum of research to address immune-mediated graft rejection, including basic research in transplantation immunology, preclinical evaluation of new therapies, and clinical trials of promising therapeutic approaches to improve short- and long-term graft survival. The major goals of DAIT-supported research in transplantation are to (1) understand the processes and mechanisms whereby the immune system recognizes and either accepts or rejects transplanted organs, tissues, and cells; (2) develop preclinical models to evaluate clinically applicable therapies to prevent and treat rejection and prolong graft survival; and (3) evaluate promising new agents and approaches in clinical trials to improve graft survival and function.

DAIT established Program Projects in Transplantation Immunology to enhance understanding of the processes involved in controlling the immune response and to apply this knowledge in the clinical setting. The goals of this research program are to identify and characterize molecules, cells, and mechanisms involved in graft rejection and to develop therapeutic regimens that facilitate successful transplantation by modulating the immune response. Projects range from basic investigations on the genetics and regulation of the immune system to clinical research projects that define immune factors affecting the success of transplantation.

Improvements in immunosuppressive therapy have dramatically reduced acute rejection and have increased the 1-year graft survival rate for all organ transplants. However, many serious side effects are associated with the use of globally immunosuppressive drugs to prevent graft rejection. Reducing these risks, while improving graft survival, is a priority in transplantation immunology. One very attractive alternative to immunosuppression is to interrupt or modify the immune response to establish specific tolerance to the graft. In FY 1999, DAIT, with cosponsorship from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the Juvenile Diabetes Research Foundation International (JDRF), established the Immune Tolerance Network (ITN), an international consortium of over 70 basic scientists and clinical investigators, to test promising treatment regimens in four clinical areas: islet transplantation, kidney transplantation, autoimmune diseases, and asthma and allergic diseases. The first clinical trial being conducted by the ITN is the "Edmonton Protocol," an experimental islet

transplantation protocol for patients with brittle type 1 diabetes. The initial study, conducted by the University of Alberta, has resulted in long-term insulin independence for 12 patients.

The ITN trial will further assess the safety and efficacy of this treatment regimen and expand the capacity for islet preparation and clinical transplantation at 10 sites in the United States, Canada, and Western Europe. Results of this international, multicenter trial will establish the "baseline" success rate for islet transplantation and facilitate the development of new tolerogenic ITN islet transplant trials. In addition, all clinical trials will have integrated studies aimed at identifying the underlying immune mechanisms involved in disease progression and therapeutic actions of the treatment regimens.

Kidney transplantation accounts for 57 percent of all transplant procedures[28] and is the preferred therapy for end-stage renal disease. To establish and coordinate multicenter clinical trials of new immunosuppressive protocols in kidney transplantation, DAIT established the Cooperative Clinical Trial in Adult Kidney Transplantation (CCTAT) in FY 1991. This program was renewed in FY 1995 and now includes 38 transplant centers throughout the United States. Among a number of important accomplishments, CCTAT trials have dramatically changed the standard of care for transplant recipients. In FY 1994, DAIT established the Cooperative Clinical Trial in Pediatric Kidney Transplantation (CCTPT). The CCTPT was renewed in FY 1999 to continue to develop clinical strategies to treat and prevent graft rejection in children, and to address the unique characteristics of the pediatric immune system. Clinical trials within the CCTPT are examining the causes of lower patient and graft survival rates in children versus adults and the effects of immunosuppressive therapy on growth retardation.

A variety of additional research programs in transplantation are also being supported. Program Projects in the Immunopathogenesis of Chronic Graft Rejection, cosponsored by the National Heart, Lung, and Blood Institute, are designed to enhance knowledge of chronic graft dysfunction. The Non-Human Primate Transplantation Tolerance Cooperative Study Group (NHPTTCSG) evaluates the safety and efficacy of novel tolerogenic regimens in preclinical models of kidney and islet transplantation. Scientists in this study group have demonstrated long-term graft acceptance using tolerogenic regimens in both kidney and islet allograft recipients. To deal with the critical shortage of rhesus macaques for this program, NIAID initiated long-term support in FY 2000 for a primate center to supply specific pathogen-free rhesus macaques to the NHPTTCSG. In addition, DAIT established a new research program in FY 2000 to evaluate the safety and efficacy of stem cell transplantation for treatment of multiple autoimmune disorders.

For more than 20 years, NIAID has supported efforts to identify and characterize antigens of the major histocompatibility complex (MHC), which are critical in matching organ donors and recipients. Until recently, knowledge about the differences in the type and frequency of transplant antigens in minority populations has been limited. This lack of knowledge has been a major factor in the

relatively poor outcomes of minority transplant recipients compared with Caucasians and has contributed to the lower number of transplants performed in minority populations. In FY 2000, NIAID led several NIH Institutes and Centers, the Centers for Disease Control and Prevention, and the JDRF in supporting the International Histocompatibility Working Group (IHWG), a network of more than 200 laboratories in more than 70 countries that will collect and share data on histocompatibility genes. The IHWG seeks to standardize and improve histocompatibility testing worldwide through the discovery, development, and distribution of information and new tissue-typing reagents. These efforts will help to ensure that transplant recipients will receive the best-matched donor organs available. In addition, NIAID support of a national workshop to identify and characterize MHC antigens in African Americans, Hispanics, and Native Americans has contributed to the development of improved methodologies for tissue-typing, thus improving donor and recipient matching. NIAID's efforts have also led to advances in the technology used for tissue typing, significantly decreasing the time necessary to perform these procedures and to transplant an organ.

Donor Organ Shortage

In 1999, 21,990 organ transplants were performed in the United States, including 12,529 kidneys, 4,700 livers, 2,185 hearts, 368 pancreata, 901 lungs, 48 heart-lung combinations, and 1,188 kidney-pancreas combinations.[29] Despite the success of transplantation programs in this country, there remains a critical shortage of donated organs. The ever-increasing waiting list for transplants has quadrupled in size since 1988 to more than 73,000 patients. In 1999, 6,125 of those patients died while awaiting a transplant. In an effort to address these issues, DAIT supports efforts to increase donation by improving donor registries, which are used to identify potential donors, and through the development and testing of educational interventions in selected populations.

To address the critical shortage of donors, DAIT also sponsors studies of alternatives to living and cadaveric donation. Xenotransplantation, the use of nonhuman organs, tissues, or cells in human transplantation, has been largely unsuccessful due to vigorous immune-mediated rejection. DAIT-supported research in xenotransplantation focuses on better understanding the human immune response to antigens present on the surface of organs or tissues from nonhuman species and the development of methods to allow rapid identification and treatment of infectious diseases that might occur by transmission of disease-causing organisms across species barriers.

With each advance in transplantation immunology comes a new set of challenges. The challenges facing transplantation are improving long-term graft survival, establishing long-term tolerance without immunosuppressive drugs, and reducing lengthy waiting lists. NIAID's basic and clinical research programs in transplantation are committed to meeting these challenges.

Minority and Women's Health

In January 1998, NIAID created the Office of Special Populations and Research Training (OSPRT). OSPRT combines the functions formerly housed in the Office of Research on Minority and Women's Health with those under the Office of Science Training and Manpower Development. Through this reorganization, NIAID recognizes the relationship between the conduct of research in populations in which health disparities continue to exist and the need to train individuals from these populations in the furtherance of its research efforts targeted to disease areas that disproportionately affect these populations.

OSPRT develops reports and sponsors activities related to the elimination of health disparities in these populations and is the focal point for collaborative efforts involving the NIH's National Center on Minority Health and Health Disparities and the Office of Women's Health. In FY 2000, OSPRT participated in NIAID's development of a strategic plan for the purpose of addressing health disparities in minority and low-income populations. The plan focuses on three goals: (1) to conduct research to identify and address health disparities among various populations affected by infectious and immunologic diseases; (2) to increase the number of minority scientists and grantees; and (3) to improve education and outreach activities for the transfer of health information to these populations. The plan is online at http://www.niaid.nih.gov/healthdisparities/niaid_hd_plan_final.pdf.

NIAID conducts research, either through its own laboratories or through funded mechanisms, on a broad spectrum of infectious, immunologic, and allergic diseases, many of which disproportionately affect women and minorities. In studying these diseases, NIAID scientists conduct basic, applied, and clinical research. In all of its clinical research, including biomedical and behavioral studies, NIAID complies with the *1993 Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research*. NIAID is proud of its accomplishments in recruiting and retaining women and minorities in clinical trials. This success is due to a multifaceted approach to working with communities to identify and overcome barriers to participation.

The diseases and health conditions in the NIAID portfolio for which gender and/or race and ethnic disparities are most evident are HIV/AIDS, other STDs, the hepatitis C virus, asthma, TB, group B streptococcus, end-stage renal disease, kidney transplantation, chronic fatigue syndrome, and SLE and other autoimmune diseases.

Minority Health Activities

Minority populations in the United States bear a disproportionate burden of sickness and disease. Many of the health problems that disproportionately afflict minorities fall within the purview of NIAID. These health problems include acquired immunodeficiency syndrome (AIDS), asthma, sexually transmitted diseases (STDs), tuberculosis (TB), autoimmune diseases, and kidney disease. NIAID has developed a comprehensive program of basic, clinical, and epidemiologic research designed to reduce the severity and prevent the occurrence of these and other conditions.

The Institute strives to include minorities in all phases of its research program, from the recruitment of patients for clinical trials to the involvement of minority researchers. NIAID

also is resolved to increase the number of minority scientists by supporting undergraduate, graduate, and postgraduate research training in immunologic and infectious diseases.

Chronic allergic conditions pose serious threats to quality of life, patient well-being, employee productivity, and school performance and attendance. The cost to the health care system is more than $10 billion annually. Over the past 15 years, asthma morbidity and mortality have increased in the United States, particularly among poor African-American and Hispanic/Latino inner-city residents. Asthma is more prevalent among minority children, and members of minority groups are three times more likely to die from this disease. Low socioeconomic status, exposure to cockroach allergens and pollutants, lack of access to medical care, and lack of self-management skills all contribute to increased morbidity from asthma. In response to the recent rise in asthma morbidity among nonwhite populations, NIAID, in collaboration with the American Academy of Allergy, Asthma, and Immunology and other professional organizations, developed clinical practice guidelines for the diagnosis, management, and prevention of allergic diseases and asthma.

In the ongoing Inner-City Asthma Study (1996-2001), NIAID and the National Institute of Environmental Health Sciences are supporting a comprehensive environmental intervention to reduce exposure to the major indoor allergens. In this 950-patient study, the baseline data show unanticipated and very high rates of sensitization to a range of indoor allergens. Preliminary data highlight many serious obstacles to allergen remediation in inner-city environments. NIAID also supports a demonstration and education research program targeted toward asthma in medically underserved, predominantly inner-city Hispanic and African-American populations. Many of the components of this program are funded through Asthma and Allergic Diseases Research Centers, located in rural and urban sites throughout the United States. NIAID supports 13 Asthma and Allergic Diseases Research Centers to carry out multifaceted basic and clinical research projects on the mechanisms of asthma and allergic diseases as well as treatment and prevention strategies. For example, one project uses nurse home visitors for self-management training and environmental interventions in high-risk infants with wheezing. Another demonstration and education project developed a unique computer-based medical and self-management training program for families of children with asthma.

Autoimmune diseases are disorders in which the immune system attacks the body's own cells, tissues, and organs. Collectively, these types of diseases afflict many millions of people in the United States. There are several autoimmune diseases that disproportionately affect minority populations. For example, systemic lupus erythematosus (SLE) is more common and more severe in African-American women and is also two times more prevalent among African-American men than among Caucasian men. Reports indicate an increased prevalence of SLE and rheumatoid arthritis among many Native American tribes, and scleroderma is found to be more prevalent in African-American women. The chronic nature of these and other autoimmune diseases leads to high medical costs and affects women's careers, families, and children.

To address the health disparities caused by autoimmune diseases, NIAID's Division of Allergy, Immunology and Transplantation (DAIT) supports Autoimmunity Centers of Excellence, a program that integrates basic and clinical research in an environment of collaboration among multiple disease specialists, including neurologists, rheumatologists, endocrinologists, gastroenterologists, and clinical immunologists. NIAID recently established the Immune Tolerance Network (ITN), a multi-institutional research program designed to conduct clinical trials of promising tolerogenic approaches; carry out integrated studies of underlying mechanisms; and develop surrogate/biomarkers of tolerance induction and maintenance in four clinical areas, including autoimmune diseases. In addition, DAIT established the Multiple Autoimmune Diseases Genetics Consortium in FY 1999, a repository of genetic and clinical data and materials collected from family members who have two or more distinct autoimmune diseases. DAIT has also joined in several program announcements in collaboration with other NIH Institutes and Centers (ICs) to stimulate research related to several specific areas of autoimmune disease with health disparities implications. These efforts include an initiative on Gender in the Pathogenesis of Autoimmunity and an initiative on Genetics, Mechanisms, and Signaling in Autoimmunity. NIAID is also currently funding an epidemiological study to investigate the prevalence of SLE in women in Africa, the Caribbean, and African-American women in the United States. The findings from this study will address the genetic and environmental factors important in the pathogenesis of this autoimmune disease.

Illnesses such as kidney failure, diabetes, leukemia, coronary heart disease, and liver disease affect millions of Americans, many of them minorities. For many of these patients, transplantation of solid organs, tissues, or cells would avert and, in some cases, reverse the severe outcomes of these diseases. Successful transplantation depends on the availability of donated organs and accurate methods to match donor and recipient human leukocyte antigens (HLA) types. HLAs, or the transplantation of antigens of humans, have a general role in regulating the immune response, and antigens are the major targets of rejection. Subtle HLA differences can go undetected by the current typing methods, yet these differences may be significant enough to trigger graft rejection. In addition, knowledge of the relevant HLA types in minority populations is incomplete and may contribute to the decreased availability of donor organs and poorer graft survival in these populations.

NIH supports numerous efforts to develop organ and bone marrow registries, to increase organ donation, and to improve HLA typing. To increase the number of minorities on the national organ transplantation registry, NIAID initiated demonstration and education research projects through community outreach programs in Louisiana and Washington. To improve HLA typing, NIAID led several NIH ICs and the Juvenile Diabetes Research Foundation International in supporting the International Histocompatibility Working Group (IHWG), a network of more than 200 laboratories in more than 70 countries that will collect and share data on histocompatibility genes. The IHWG seeks to standardize and improve histocompatibility testing worldwide

through the discovery, development, and distribution of information and new tissue-typing reagents. These efforts will help to ensure that transplant recipients receive the best-matched donor organs available.

In addition, NIAID support of a national workshop to identify and characterize major histocompatibility complex antigens in African Americans, Hispanics, and Native Americans has contributed to the development of improved methodologies for tissue typing, thus improving donor and recipient matching. NIAID's efforts also have led to advances in the technology used for tissue typing, significantly decreasing the time necessary to perform these procedures and to transplant an organ.

Underdiagnosis of primary immunodeficiencies is believed to be a major problem, especially in minority populations in which prevalence estimates appear to be disproportionately low compared to Caucasians. Although these racial differences may have an underlying genetic basis, preliminary data suggest that primary immunodeficiency diseases are not being recognized in U.S. minority populations. Lack of access to consistent health care, in addition to inaccurate expectations among health care providers, may foster underdiagnoses of these disorders among minority populations. In FY 2000, NIAID provided support for a new research project to test the hypothesis that primary immunodeficiency diseases are not being fully recognized in minorities. Utilizing an urban hospital setting with a large Hispanic and African-American patient population, occurrence of these disorders is being retrospectively estimated and prospectively verified with clinical tests. A newly developed screening instrument that takes advantage of multiple international classification of disease codes indicative of immunodeficiencies is being used. In addition, this research project involves the testing of educational materials targeted at minorities and involves the community of minority health care providers. The educational component, which can be widely distributed, is expected to increase awareness and improve diagnosis and early detection of primary immunodeficiencies in these populations.

In FY 1999, NIAID established the Immune Tolerance Network, an international consortium of more than 70 basic scientists and clinical investigators, to test promising tolerogenic treatment regimens in four clinical areas: islet transplantation, kidney transplantation, autoimmune diseases, and asthma and allergic diseases. The clinical research program will evaluate new tolerance induction strategies to treat asthma and multiple autoimmune diseases, including diseases, such as SLE, that disproportionately afflict minority women.

NIAID's microbiology and infectious diseases segment of its scientific agenda includes intramural and extramural research to control and prevent diseases caused by virtually every infectious agent. One of the Institute's primary goals is to extend the impact of vaccines in preventing disease.

TB continues to be a severe problem in minority populations even though the number of new cases has been plateauing. In 1998, approximately 75 percent of the active cases of TB were reported among racial and ethnic minorities. The disproportionate impact of TB among minorities is related to many

socioeconomic factors, such as overcrowded living conditions, and inadequate treatment and/or compliance with TB chemotherapy.

In response to this continuing problem, NIAID has increased its efforts to develop new drugs, to promote new treatment regimens with existing drugs, and to develop a vaccine. NIAID has done this by supporting new initiatives, attracting researchers to the field of TB research, and creating a Tuberculosis Research Unit.

In collaboration with the National Heart, Lung, and Blood Institute, NIAID is funding an initiative to support the development of improved animal models for TB, particularly in the areas of persistence and reactivation of disease, because most cases of TB arise in persistently infected individuals (roughly 2 billion people globally). In collaboration with the Fogarty International Center, NIAID supports seven supplemental training awards to improve global health research and public health capacity for responding to the TB epidemic.

NIAID presented a blueprint for TB vaccine development at the 1998 International Symposium for Tuberculosis Vaccine Development and Evaluation. The *TB Blueprint Report* outlines the specific steps needed to develop improved TB vaccines. A trans-Department of Health and Human Services Task Force, which includes representation from NIAID, is overseeing implementation of the *TB Blueprint Report*.

The current epidemic of STDs in the United States disproportionately affects minorities. For example, although African-American and Hispanic/Latina women comprise only 17 percent of the total female population in the United States, they represent 33 percent of the consultations for pelvic inflammatory disease (PID), a disease of the upper reproductive tract caused primarily by sexually transmitted bacterial infections. NIAID STD research emphasizes the impact of STDs on women and the relationship between STDs and HIV infection. The Institute's ongoing efforts in STD research include support for seven STD Cooperative Research Centers that address topical microbicides and a myriad of STD-related issues, as well as six program project grants to develop topical microbicides.

Emerging infectious diseases may pose a continuing or even a growing threat in the United States in coming years. NIAID supports basic and applied research on the causes of and treatments for infectious diseases and has developed a Research Agenda for Emerging Infectious Diseases to provide an integrated and proactive research strategy to address this problem. As part of this agenda, NIAID supports four Hepatitis C Cooperative Research Centers that conduct basic and clinical research studies.

In collaboration with an expert panel, NIAID has developed a *Framework for Progress for Hepatitis C*. This document defines the major basic and clinical research objectives, questions, resources, and tools needed to achieve the Institute's research goals related to hepatitis C. NIAID also held a conference to address the incidence of hepatitis C in African Americans and to discuss issues such as the failure of conventional treatment modalities in this population.

Today, racial and ethnic minorities account for more than 60 percent of the reported AIDS cases in the United States. The majority of HIV-infected women (80 percent) are among

African-American or Hispanic populations. As a consequence, the majority of HIV-infected children are African American or Hispanic/Latino. NIAID addresses minority issues in HIV disease in four major areas: treatment research, epidemiologic research, vaccine and prevention research, and infrastructure development and training of minority researchers.

The NIAID national clinical trials program includes the Adult AIDS Clinical Trials Group, the Pediatric AIDS Clinical Trials Group, and the Terry Beirn Community Programs for Clinical Research on AIDS. All of these networks strive to ensure that a sufficient proportion of minority subjects are enrolled into clinical trials so that the results of the research may be generalized to the affected HIV population at large. NIAID-supported epidemiology studies include the Women and Infants Transmission Study and the Women's Interagency HIV Study, which operates in tandem with the Multicenter AIDS Cohort Study. Enrollment of people of minority background in these studies is approximately 86, 80, and 15 percent, respectively.

The HIV Network for Prevention Trials (HIVNET) has a broad-based agenda that includes trials of vaccines, topical microbicides, STD treatment, behavioral interventions, and approaches to prevent mother-to-infant transmission of HIV/AIDS. The HIVNET Vaccine Preparedness Study is evaluating strategies for conducting future HIV vaccines and other preventive measures in populations at greater risk for contracting HIV in the United States.

NIAID is developing an AIDS vaccine communication campaign to increase awareness of AIDS vaccine research before the initiation of an efficacy study. Part of this campaign will include developing messages that will promote and enhance the participation of high-risk communities, including minorities, in NIAID-sponsored vaccine trials.

The Institute helped support a new NIH Spanish-language newsletter, *El Pulso de la Salud: Información de los Institutos Nacionales de la Salud*, which is distributed nationwide. NIAID serves on the NIH committee that publishes the newsletter and contributed articles on HIV/AIDS and STDs.

In October 1999, the NIH launched a major Curriculum Supplement Series for kindergarten through grade 12. NIH will distribute the series to teachers throughout the United States free of charge to improve science literacy and to foster students' interest in science. The NIAID contribution to the curriculum is called "*Emerging and Re-Emerging Infectious Diseases*" and targets grades 9 through 12.

Increasing the participation of under-represented minority investigators in virtually all fields of biomedical research is a continuing NIH and NIAID priority. NIAID supports a variety of minority programs for biomedical research, encompassing high school through postdoctoral training.

In October 2001, NIAID will sponsor its fifth *Bridging the Career Gap for Underrepresented Minority Scientists* workshop, which was established in 1993, to nurture the careers of young minority investigators currently funded by the Institute under various minority training and research supplemental awards.

Due to the success of the *Bridging* program, other Institutes are now duplicating it with similar initiatives.

In February 2001, NIAID held its 23rd Introduction to Biomedical Research Program (IBRP) (http://www.niaid.nih.gov/osprt/ibrp.htm). This initiative grew out of the need to increase the number of minority scientific researchers in the United States. The program informs academically talented college juniors, graduating seniors, and first-year graduate or medical students from underrepresented minority groups about career opportunities in the broad field of biomedical research.

Twenty years after starting the program, NIAID is beginning to see the long-term effects of this innovative program. Several IBRP participants have received NIH grants, been tenured in academia, entered the Institute's intramural training programs, and joined the extramural staff.

NIAID recognizes that it must not only maintain but also expand its commitment to improve minority health and attract more capable minority researchers to allergic and infectious disease research. A healthy citizenry is an essential part of a productive society. NIAID will continue its efforts to increase the participation of ethnic minorities in its crucial research agenda and seek to eliminate health disparities wherever they occur in our nation's population.

Women's Health Activities

Women in the United States and around the world bear a disproportionate burden of many immunologic and infectious diseases. Women's health concerns during the past decade have been of paramount concern in the broadest biomedical, political, and social sense. Our nation recognizes the importance of women's health and, more specifically, the important contributions of culture, ethnicity, race, socioeconomic background, geographic location, and other social and economic factors to women's health status. It is imperative that we understand that women's health is a reflection of multiple elements contributing to the overall quality of women's lives—and men's lives—in the United States today.

Women and men may, and often do, require different treatments or interventions in their health care. NIAID researchers are paying particular attention to all aspects of women's health, including STDs, AIDS, and HIV in women; immunologic disorders; SLE; and asthma.

NIAID has an extensive research program on STDs that includes five major goals: (1) prevention of infertility; (2) prevention of adverse pregnancy outcomes; (3) prevention of reproductive tract tumors; (4) prevention of HIV infection; and (5) prevention of other adverse effects of STDs. The control of many STDs is complicated by the frequency of asymptomatic infections; the lack of safe, effective vaccines; the cost and technical difficulty of available diagnostic tests; the expense of single-dose oral therapies; and the absence of effective methods that women can use to protect themselves from STDs. NIAID supports research aimed at developing and evaluating new diagnostic tests for STDs that will be rapid, inexpensive, and easy to use. These tests will be used in screening for STDs, particularly to detect infections that do not produce symptoms. NIAID's multidisciplinary research strategy includes basic science,

vaccine development, behavioral science, development of topical microbicides, and development of rapid and inexpensive diagnostic tests.

Topical microbicides are preparations used intravaginally or intrarectally to inactivate HIV and other STDs and are critically important for controlling HIV infection. An inexpensive, reliable, female-controlled method for preventing HIV and other STDs is needed so that women can protect themselves. In FY 2000, BufferGel, a novel microbicide, was shown to be safe and acceptable in a multisite international phase I trial funded by NIAID. Results of a phase I trial of low-risk women in the United States and in international settings have shown that BufferGel was nontoxic and well tolerated. Research will be conducted to determine the effectiveness of BufferGel in preventing HIV infection.

NIAID's research on HIV infection in women is focused on defining HIV disease in women, studying HIV-associated conditions that specifically affect women, defining the mechanisms of maternal-infant and mucosal (sexual) transmission, and developing vaccines and prevention strategies to protect against sexual transmission.

Autoimmune diseases include insulin-dependent diabetes, SLE, multiple sclerosis, and other illnesses in which the immune system attacks the body's own tissues. Although many autoimmune diseases are rare, collectively they afflict more than 5 percent of the U.S. population and a disproportionate number of women, particularly women of working age and in their childbearing years.

Organ transplants have saved the lives of thousands of patients and have improved the quality of life for tens of thousands more. Almost half of all transplant patients are women. Despite major advances in the field, many transplants fail within the first year. NIAID is conducting extensive research to increase the percentage of successful transplants, including drug therapies derived from immune-system responses against an organ transplant.

Asthma, an inflammatory disease of the lungs that causes difficulty in breathing with associated wheezing and coughing, though serious, is rarely fatal. In childhood, boys outnumber girls for asthma hospital admission 2 to 1, but from ages 20 to 50, women outnumber men 3 to 1. There is evidence that asthma may be related to women's hormonal changes. NIAID currently supports 13 Asthma and Allergic Diseases Research Centers throughout the country. These Centers operate eight Asthma Demonstration and Education Research projects that develop innovative methods for preventing and treating asthma among underserved populations, particularly ethnic minorities. The discovery of possible asthma-related genes opens the door to diagnostic tests that could potentially identify individuals susceptible to asthma and determine optimal treatment for them.

Research supported by NIAID has led to the development of promising vaccine candidates for chlamydia, genital herpes, human papillomavirus, group B streptococcal infection, asthma, and some cancers. In the future, NIAID will continue to support research on health issues involving women, and as with all biomedical research issues, the results may have important implications for society as a whole.

Genomics

Division of Microbiology and Infectious Diseases

Advances in molecular biology have led to remarkably fast and accurate methods for sequencing the genomes of disease-causing microorganisms. Genome sequencing reveals the lineup of paired chemical bases that make up the pathogen's DNA, the language of life. The potential payoffs of sequencing pathogens are enormous. Sequence information is being exploited in the following ways:

- To locate targets for vaccine and drug development,
- To identify mutations that contribute to drug resistance,
- To compare the genomes of variant strains to note differences that may affect the antigenicity or virulence of the microbe, and
- To trace microbial evolution.

When scientists identify genes that are unique to a particular microbe, drugs can be targeted to these genes, and the products of these genes can be incorporated into experimental vaccines. Furthermore, strategies can be devised to counteract genetic mutations that cause a microbe to become drug resistant. Once virulence genes are found, researchers can attempt to disable them. Moreover, genetic variations detected in different strains of the same pathogen can be used to study the population dynamics of these strains, such as the spread of a virulent form of a pathogen in a susceptible population. Finally, understanding the genetic basis for both virulence and drug resistance may also help predict disease prognosis and influence the type and extent of patient care and treatment.

Recognizing the tremendous benefits of genome sequencing, NIAID has funded projects to sequence the full genomes of a number of medically important microbes, including the bacteria that cause tuberculosis, gonorrhea, chlamydia, and cholera. In addition, NIAID collaborates with other funding agencies to sequence the larger genomes of protozoan pathogens such as that of the organism causing malaria. Many of these microbes have been completely sequenced and are now being annotated and analyzed. During annotation, each gene's position or placement on the genome is determined. This information is further analyzed to provide insight on important features of the genome that may affect the biology of the microbe and its ability to cause disease. Sequence information and annotation data are continually made available to the scientific community by means of publicly accessible web sites.

NIAID is committed to continuing its support to sequence the genomes of microbes as well as increasing its support for functional genomics, decoding sequence information, and determining its functional sequence. NIAID is committed to facilitating the access and distribution of genomic resources and technologies to the research community for functional genomic analysis of microbial pathogens, as well as to supporting the development of bioinformatic and computational tools to allow investigators to store and manipulate sequence and functional data. NIAID's web site on pathogen genomics provides details on currently supported genome-sequencing projects, and on policies and priorities for large-scale genome-sequencing projects and related genomic activities (http://www.niaid.nih.gov/dmid/genomes/).

The following is a list of NIAID-supported large-scale pathogen genome-sequencing projects in FY 2000:

Organism	Disease	Organism	Disease
• *Aspergillus fumigatus*	aspergillosis	• *Pneumocystis carinii*	pneumonia, opportunistic disease
• *Bacillus anthracis*	anthrax		
• *Brucella suis*	brucellosis	• *Rickettsia typhi*	typhus
• *Buckholderia mallei*	glanders	• *Salmonella typhi*	typhoid fever
• *Chlamydia pneumoniae*	pneumonia	• *Salmonella typhimurium*	food-borne diseases, gastritis
• *Chlamydia trachomatis*	genital and chlamydia infections, trachoma	• *Shigella flexneri* 2a	shigellosis, hemolytic uremic syndrome
• *Coxiella burnetii*	Q fever		
• *Cryptococcus neoformans*	cryptococcosis	• *Staphylococcus aureus*	surgical and wound infections, pneumonia, toxic shock syndrome
• *Cryptosporidium parvum*	food- and water-borne diseases, gastritis		
• *Ehrlichia phagocytophila*	ehrlichiosis		
• *Entamoeba histolytica*	dysentery	• *Staphylococcus epidermidis*	bacteremia
• *Enterococcus faecalis*	nosocomial infections		
• *Escherichia coli* 0157:H7	gastritis, hemolytic, uremic syndrome	• *Streptococcus pneumoniae*	pneumonia, meningitis
• *Escherichia coli* K1	meningitis	• *Streptococcus pyogenes*	pharyngitis, skin infections, necrotizing fascitis, streptococcal toxic shock syndrome, rheumatic fever
• Several strains of pathogenic *Escherichia coli*	gastritis		
• *Giardia lamblia*	giardiasis		
• *Haemophilus ducreyi*	chancroid	• *Treponema pallidum*	syphilis
• *Legionella pneumophila*	Legionnaire's disease	• *Trypanosoma brucei*	trypanosomiasis
• *Leishmania major*	cutaneous leishmaniasis	• *Trypanosoma cruzi*	Chagas' disease
• *Mycobacterium avium*	pulmonary disease, disseminated disease, opportunistic disease	• *Ureaplasma urealyticum*	pelvic inflammatory disease
		• *Vibrio cholerae*	cholera
• *Mycobacterium tuberculosis*	tuberculosis	• *Wolbachia*	endosymbiont of filarial nematodes and insect vectors
• *Neisseria gonorrhoeae*	gonorrhea		
• *Nematode species*	helminthiases	• *Yersinia enterocolitica*	gastritis
• *Plasmodium falciparum*	malaria	• *Yersinia pestis*	plague

Division of Allergy, Immunology and Transplantation

Genetic maps of human DNA give clinicians and researchers tremendous descriptive and predictive power, enabling them to determine how cells grow, what traits they express, and what messages they convey to other cells. The human immune system is composed of complex networks of interacting cells, each programmed by precisely scripted genes. Underlying each immune response to a disease is a multistepped pathway of interacting molecules rooted in an individual's unique genomic characteristics. The immune system plays a critical role in diseases, such as rheumatoid arthritis, hay fever, contact dermatitis, insulin-dependent or type 1 diabetes, systemic lupus erythematosus, and graft rejection. Each of these diseases has an underlying genetic component.

Genomic research supported by NIAID's Division of Allergy, Immunology and

Transplantation (DAIT) is yielding insights into the functional and structural dimensions of immune system regulation; hypersensitivity and inflammation in diseases such as asthma; dysregulation of immune responses that result in autoimmune disease; and basic mechanisms of immune tolerance and graft rejection of transplanted solid organs, tissues, and cells. This research is important in the following areas:

- **Allergic diseases, including asthma.** DAIT supports research into the genetics of asthma, hypersensitivity, inflammation, and T-cell mediation, which enables us to understand the underlying immune mechanisms resulting in improved diagnoses, prevention strategies, and effective treatments. Through genomic research, DAIT-supported investigators discovered that one cytokine—interleukin-4 (IL-4), which is produced by helper T cells and mast cells—stimulates antibody production by B cells in a series of reactions involving several genes. Further studies on IL-4 may provide a marker for measuring the risk and severity of asthma.

- **Autoimmune diseases.** DAIT supports research on type 1 diabetes and other autoimmune disorders, which are polygenic diseases, resulting from more than a single gene. Recent developments in genomics—such as high-resolution DNA analysis and bioinformatics—are making it possible to map complex causal genomic relations that point to the source of these pathologies. One approach compares the genes of individuals with an autoimmune disease to healthy individuals to identify misaligned genes, or single nucleotide polymorphisms (SNPs), that may be the underlying cause of disease. Between 10 and 20 distinct loci on the human genome may be responsible for susceptibility to type 1 diabetes. SNP discovery of polymorphisms associated with type 1 diabetes will increase our ability to predict, diagnose, and treat this disease.

- **Transplantation.** DAIT-supported research on the genetics of graft rejection and immune tolerance is plowing new ground in the transplantation of cells and genes for the prevention and treatment of disease. Today, for example, genome-based techniques are being developed to provide patient-tailored treatments to correct genetic defects, reeducate cells to strengthen their resistance to cancer, or modify the cells of transplant recipients to be more tolerant of foreign tissue.

- **Basic immunology research.** DAIT invests substantially in basic research on immune genetics. Basic immunology extends our understanding of the properties, interactions, and functions of the cells that comprise the immune system and elucidates the genetic aspects of immune system regulation and many essential structural aspects of immune biology. Recent breakthroughs in the basic science of immunogenetics inform clinical immunology, which may lead to new biotechnology-based therapies. Examples of basic immunology research supported by DAIT include the following:

  – Signal transduction, the use of large-scale gene and protein-expression-analysis tools to describe pathways of cellular activation;

- Discovery of anti-inflammatory and immunosuppressive agents using gene-based screening methods to determine a person's sensitivity to a drug; and

- Analysis of genomic databases of T-cell receptors and immunoglobulin gene sequences to link structural, functional, and clinical information.

DAIT supports several multicenter research efforts with major genomic efforts aimed at the underlying mechanisms of immune-mediated disease.

Multicenter Research Efforts

- **Multiple Autoimmune Disease Genetics Consortium (MADGC).** Established in FY 1999, MADGC is a collaborative effort to establish a repository of genetic materials and clinical data collected from 400 multiplex families (three or more affected individuals) affected by two or more of the following autoimmune diseases: rheumatoid arthritis, juvenile rheumatoid arthritis, type 1 diabetes, multiple sclerosis, systemic lupus erythematosus, autoimmune thyroid disease, psoriasis, and inflammatory bowel disease. Data and samples from these families are made available to researchers for studies to identify and characterize genes involved in the susceptibility or resistance to autoimmune diseases. For more information, see http://www.madgc.org/.

- **North American Rheumatoid Arthritis Consortium (NARAC).** NIAID, the Arthritis Foundation, and the National Institute of Arthritis and Musculoskeletal and Skin Diseases are supporting a collaborative effort to identify the genes that predispose individuals to rheumatoid arthritis. Researchers participating in NARAC are collecting medical information and genetic material (DNA) from 1,000 families nationwide in which two or more siblings developed rheumatoid arthritis between 18 and 60 years of age and have at least one surviving parent. This resource should allow investigators to identify a number of genes that are associated with the development of rheumatoid arthritis. Identifying these genes should provide insight into the pathogenesis of this disease and could lead to the development of new prevention and treatment strategies.

- **International Histocompatability Working Group (IHWG).** NIAID, with cosponsorship from the National Cancer Institute, the National Institute of Diabetes and Digestive and Kidney Diseases, the National Human Genome Research Institute, the NIH National Library of Medicine's National Center for Biotechnology Information (NLM/NCBI), and the Centers for Disease Control and Prevention, supports the IHWG, a network of more than 200 laboratories in more than 70 countries. The IHWG focuses on applying new molecular techniques to population-based studies of HLA genes. Recent advances in genomics have provided new tools to explore HLA polymorphisms and their roles in immunity, disease susceptibility, and transplantation. This multicenter project is developing reagents for defining sequence variations of HLA class I and II genes and HLA-related microsatellite and SNPs. Over time this work will bridge the gap between serological and genomic definitions of HLA alleles. Genomic techniques developed by IHWG

investigators revealed a greater diversity among HLA alleles than was previously detected by conventional serological methods. Such findings have important implications for a variety of research areas, ranging from human evolution to clinical immunology.

In addition, the IHWG is establishing a centralized, international genomics database to serve as a repository of HLA sequence polymorphisms and as a platform for future basic and clinical research. This database will be housed at the NLM/NCBI, which has committed the resources to initiate and maintain the database for public access. One project of the IHWG will establish an international bone marrow registry to facilitate more accurate matching of transplant donors to recipients. The data generated will also provide a greater understanding of HLA diversity in many ethnic groups.

- **Immune Tolerance Network (ITN).** The ITN, an international consortium of more than 70 basic scientists and clinical investigators, is exploring new approaches to selectively block or prevent the initiation of detrimental immune responses. The potential impact of tolerance induction on human health is great, encompassing a broad range of immune-mediated diseases, including autoimmune diseases such as type 1 diabetes, rheumatoid arthritis, and multiple sclerosis; asthma and allergic diseases; and graft rejection in kidney, pancreas, heart, lung, bone marrow, and cell transplantation. Genomics research now under way at the ITN will enable new therapeutic strategies in tolerance induction.

Federal Government/Industrial Collaboration

DAIT, in partnership with Roche Pharmaceuticals and Motorola, is supporting research projects that use bioinformatics to analyze clinical and gene-expression data that have been combined into one seamless database. This work, which involves clinical patient data and rapid throughput-polymerase chain reaction (RT-PCR), gene chip, and proteomics data, aims to determine the underlying immune mechanisms responsible for the initiation and progression of end-stage renal disease (kidney failure), as well as acute and chronic rejection or long-term kidney-graft survival. This research models disease processes through a combination of sophisticated data-mining and hypothesis-based research to identify early markers of kidney-graft acceptance, rejection, and function. This government-industry collaborative effort serves as a model for future programs in other immune-mediated diseases, particularly autoimmune disorders.

Bioengineering, Bioinformatics, and Other Emerging Technologies

Bioengineering, bioinformatics, and other emerging technologies are interdisciplinary and enabling fields of research. Bioengineering, for instance, combines physics, chemistry, and mathematics, as well as basic engineering principles, to enhance the study of biology, medicine, behavior, and health. It creates new knowledge by applying engineering principles and techniques. This knowledge supports development of new biologics, materials, and devices for the diagnosis, prevention, and treatment of disease. Bioinformatics and its partner discipline, computational biology, involve the application of computer sciences and advanced mathematics to enable integration and pattern recognition in diverse sorts of biological, medical, behavioral, or health data. The unique tools and perspectives of bioengineering, bioinformatics, and computational biology are critical components of immunology research today. They are becoming fully integrated into many aspects of NIAID's basic and clinical activities. Examples of NIAID research in these areas include the following:

- **Mass spectrometry for high-throughput peptide characterization.** NIAID-funded scientists are developing chemical measurement instruments for the sequence analysis of peptide antigens presented in the major histocompatibility complex. This research promises a high-throughput method to study self-peptides. Understanding how the body distinguishes itself from foreign (possibly harmful) agents is relevant to all immune-mediated diseases.

- **Modular gene assembly.** A new system is being developed for engineering genes on the basis of their binding and activation properties, as well as chimeric features. This research will enable the formation, selection, and assembly of genes based on individual functional traits, which may lead to novel therapeutic compounds, such as custom antibodies or immunosuppressants.

- **Bioinformatics for lead compound selection.** Computers enhance our ability to characterize complex molecules and understand binding patterns (e.g., ligand-receptor interaction), which may lead to possible new anti-inflammatory and immunosuppressive agents.

- **A drug-delivery system to treat immune-mediated diseases.** NIAID-funded investigators are developing an active, silicon-based delivery system that may be a useful tool for vaccines, antibiotics, and anti-inflammatory agents. Controlled drug delivery has the advantage of providing stable drug bioavailability tailored to the needs of individual patients, while minimizing patient risk.

- **Whole-organism imaging of immune response.** The ability to monitor the precise ways in which T cells accumulate in lymphoid organs, such as the liver, kidney, and bowel, or in the central nervous system holds important keys to understanding autoimmune disease. One NIAID-funded project is combining nuclear and magnetic resonance imaging to generate whole-body images of research subjects. Already, these investigators have prototyped a system for whole-body scanning of the mouse. In addition, the monitoring of cell movement can provide an early warning of acute graft rejection in organ transplantation. NIAID-funded investigators are applying magnetic

resonance imaging to detect accumulation of labeled T cells and macrophages in a living organism and are perfecting agents that show the contrast between cells and background tissue.

The tools and techniques of bioengineering and bioinformatics discussed here are becoming even more crucial to biomedical research with the emergence of genomics. Genome maps provide a guidebook to the human body that could become crucial in diagnosing and treating immune-mediated and other diseases. But researchers and clinicians require a whole new set of tools to manage all the information that is generated through genomic research and to follow the genomic map to the true sources of disease and its treatment. Thus, NIAID supports the following areas of genome-based research:

- First, for many years, NIAID-supported investigators have conducted studies to explain the genetic origins and variation relevant to immune-mediated diseases. Projects focus on the development of tools to improve identification of SNPs (single nucleotide polymorphisms) and the maintenance of protein databases, which are of broad interest to immunologists.

- Second, genomic research generates massive amounts of data, which are cumbersome to store and even more challenging to analyze. Through bioinformatics, these data may be archived and made more accessible to diverse clinical and basic research communities.

- Finally, many NIAID-funded researchers are now shifting their attention to the proteins expressed by genes. Whereas the entire makeup of the human body can be contained in approximately 30,000 genes, these genes express themselves functionally through 3 to 5 million proteins, each of which has a distinct role and function. The rapidly emerging field of proteomics will soon provide a wealth of information about each protein's function, domain structure, subcellular location, posttranslational modifications, variants, and similarities to other proteins. NIAID is assisting researchers in developing a new arsenal of tools to monitor and manipulate gene expression.

References

1. UNAIDS/WHO. AIDS Epidemic Update: December 2000.
2. WHO. World Health Report 2000.
3. WHO. (1995-2005). Tuberculosis Fact Sheet.
4. CDC. NNIS Semiannual Report. June 2000.
5. Whitney CG et al. Increasing prevalence of multidrug-resistant *Streptococcus pneumoniae* in the United States. *N Engl J Med* 2000: 1917-1924.
6. WHO. Division of Control of Tropical Diseases—Malaria Control—Burden and Trends.
7. WHO. Global Strategy for Containment of Antimicrobial Resistance.
8. WHO. Food Safety Programme in WHO.
9. Wong JB, McQuillan GM, McHutchinson JG, Poynard T. Estimating future hepatitis C morbidity, mortality and costs in the United States. *Am J Public Health* October 2000; 90(10): 1562-1569.
10. NHANES II, the Second National Health and Nutrition Examination Survey. *J Allergy Clin Immunol* 1987; 80: 669-679.
11. Nathan RA, Meltzer EO, Selner JC, Storms W. Prevalence of allergic rhinitis in the United States. *J Allergy Clin Immunol* 1997: 99: S808-814.
12. Prevalence of Selected Chronic Conditions: United States, 1990-1992. Series 10: Data from the National Health Survey, CDC, January 1997; DHHS Pub. No. 97-1522.
13. In: Allergy, Principles, and Practice, 4th edition. E Middleton et al., eds. Mosley, St. Louis, 1993, 1581.
14. CDC. National Center for Health Statistics. *Vital and Health Statistics Series* 1996; Vol. 13, No. 134.
15. *Pediatr Allergy Immunol* 1992; 3: 67-78.
16. Sicherer SH, Muñoz-Furlong A, Burks AW, Sampson HA. Prevalence of peanut and tree nut allergy in the US determined by a random digit dial telephone survey. *J Allergy Clin Immunol* 1999; 103: 559-562.
17. AAAAI Board of Directors. Anaphylaxis in schools and other child-care settings. *J Allergy Clin Immunol* 1998; 102: 173-176.
18. Sampson HA, Mendelson L, Rosen JP. Fatal and near-fatal anaphylactic reactions to food in children and adolescents. *N Engl J Med* 1992; 327: 380-384.
19. *Mayo Clin Proc* 1994; 69: 16-23.
20. CDC. *MMWR* December 4, 1998; 47(47): 1022-1025.
21. National Health Interview Survey 1994.
22. National Hospital Discharge Survey 1994.
23. CDC. CDC Surveillance Summaries, April 24, 1998; *MMWR* 1998; 47, No. SS-1.
24. CDC (1993-1994 data). CDC Surveillance Summaries, April 24, 1998; *MMWR* 1998; 47, No. SS-1.
25. Gergen PJ, Mullally DI, Evans R. National survey of prevalence of asthma among children in the United States, 1976 to 1980. *Pediatrics* 1988; 81: 1-7.
26. CDC. CDC Surveillance Summaries, April 24, 1998; *MMWR* 1998; 47, No. SS-1.
27. United Network for Organ Sharing 2000. Retrieved January 7, 2001, from the World Wide Web: http://www.unos.org/Frame_default.asp?Category=Newsdata.
28. Status of NIH-Sponsored Basic and Clinical Research on Transplantation. Retrieved from the World Wide Web: http://www.niaid.nih.gov/publications/new/WhitePaper_on_Transplantation_final.pdf.
29. 1999 Annual Report of the U.S. Scientific Registry for Transplant Recipients and the Organ Procurement and Transplantation Network: Transplant Data: 1989-1998. U.S. Department of Health and Human Services, Health Resources and Services Administration, Office of Special Programs, Division of Transplantation, Rockville, MD; UNOS, Richmond, VA. Retrieved January 7, 2001, from the World Wide Web: http://www.unos.org/frame_Default.asp?Category=anrpt.

National Advisory Allergy and Infectious Diseases Council

The National Advisory Allergy and Infectious Diseases Council is composed of both scientists and laypersons. The Council makes final recommendations on the scientific merit of NIAID-assigned applications for research grants, cooperative agreements, and awards for research training activities. Review by the Council is the final step in the National Institutes of Health peer review process. Council recommendations are based both on scientific merit, as judged by the scientific review groups, and on the relevance of the proposed study to the Institute's programs and priorities. Applications reviewed relate to all activities within the NIAID research mission, including the fields of immunology, allergic and immunologic diseases, transplantation immunology, microbiology and infectious diseases, and AIDS and AIDS-related conditions. Through its subcommittees, the Council conducts concept clearances and advises NIAID on general policy.

The National Advisory Allergy and Infectious Diseases Council roster is located at the web site http://www.niaid.nih.gov/facts/council.htm.

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Acquired Immunodeficiency Syndrome Research Review Committee

In its role within the National Institutes of Health (NIH) peer review system, the Acquired Immunodeficiency Syndrome (AIDS) Research Review Committee advises the Director, NIH, and the Director, NIAID, with respect to programs and activities in the areas of AIDS as well as the prevention and treatment of the major opportunistic infections associated with AIDS. The Committee provides a primary review of selected grant applications, cooperative agreements, and contract proposals for special research and training programs. These include program projects and centers, institutional National Research Service Awards, conference grants, and special developmental award programs in AIDS-related areas. The Committee recommends ratings for those applications and proposals that it determines to have significant and substantial scientific merit and advises the Institute Director on the development of new programs in the above-mentioned scientific areas.

The AIDS Research Review Committee roster is located at the web site http://www.niaid.nih.gov/facts/revcom.htm.

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AIDS Research Advisory Committee

The AIDS Research Advisory Committee is mandated by Public Law 92-463, the Health Omnibus Programs Extension of 1988 (HOPE legislation), which was signed into law on November 4, 1988. The Committee advises and makes recommendations to the Director, NIAID, and to the Director, Division of Acquired Immunodeficiency Syndrome (DAIDS), in all areas of biomedical research on HIV infection and AIDS related to the mission of DAIDS, including pathogenesis, natural history, and transmission of HIV disease, and to those efforts that support progress in its detection, treatment, and prevention.

The Committee provides broad scientific, programmatic, and budgetary advice on all aspects of HIV-related research supported by NIAID, including fundamental basic and clinical research, discovery and development of vaccines and other preventive interventions, and training of researchers in these activities. This includes the review of progress and productivity of ongoing efforts, assistance in identifying critical gaps/obstacles to progress, and approval of concepts for new initiatives.

The AIDS Research Advisory Committee roster is located online at http://www.niaid.nih.gov/facts/arac.htm.

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AIDS Vaccine Research Committee

The AIDS Vaccine Research Committee, a working group established in February 1997, assists the NIH in developing a comprehensive research program for the purpose of expediting the discovery and development of an AIDS vaccine. The group advises the vaccine research programs at the NIH with regard to scientific opportunities, gaps in knowledge, and future directions of research. The Committee, which reports to the NIAID Council, is chaired by Dr. David Baltimore and is composed of individuals with expertise in immunology, structural biology, virology, animal models, and vaccine development.

The AIDS Vaccine Research Committee roster is located at the web site http://www.niaid.nih.gov/aidsvaccine/AVRCR.htm.

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Allergy, Immunology, and Transplantation Research Committee

The Allergy, Immunology, and Transplantation Research Committee advises the Director, NIH, and the Director, NIAID, with respect to programs and activities in the areas of allergy, clinical immunology, immunopathology, immunobiology, immunogenetics, immunochemistry, and transplantation biology. The Committee provides primary review of grant applications and special research programs. These include program projects, institutional National Research Service Awards, conference grants, and special developmental award programs. The Committee recommends ratings for those applications that it determines to have significant and substantial scientific merit.

The Allergy, Immunology, and Transplantation Research Committee roster is located at the web site http://www.niaid.nih.gov/facts/revcom.htm#CVH16.

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National Institute of Allergy and Infectious Diseases
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Microbiology and Infectious Diseases Research Committee

The Microbiology and Infectious Diseases Research Committee advises the Director, NIH, and the Director, NIAID, with respect to programs and activities in microbiology and infectious diseases. Specialized areas of concern include molecular biology, microbial chemistry, parasitology, virology, bacteriology, mycology, vaccine development, and antimicrobial chemotherapy. The Committee provides a primary review of grant applications, cooperative agreements, and contract proposals for special research programs. These include program projects and centers, institutional National Research Service Awards, conference grants, and special developmental award programs in the aforementioned areas. The Committee recommends ratings for applications and proposals that it determines to have significant and substantial scientific merit and advises the Institute Director on development of new programs in the above-mentioned scientific areas.

The Microbiology and Infectious Diseases Research Committee roster is located online at http://www.niaid.nih.gov/facts/revcom.htm#SAL32.

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Department of Microbiology and Immunology
School of Medicine
University of Texas Medical Branch
Galveston, Texas

Karla A. Kirkegaard, Ph.D. (2001)
Associate Professor
Department of Microbiology and Immunology
School of Medicine
Stanford University
Stanford, California

Jean C. Lee, Ph.D. (2003)
Associate Professor
Department of Medicine
Channing Laboratory
Brigham and Women's Hospital
Harvard Medical School
Boston, Massachusetts

Anna Suk-Fong Lok, M.D. (2002)
Professor
Division of Gastroenterology
Department of Internal Medicine
University of Michigan
Ann Arbor, Michigan

Thomas G. Mitchell, Ph.D. (2003)
Associate Professor
Department of Microbiology
School of Medicine
Duke University Medical Center
Durham, North Carolina

Anne Moscona, M.D. (2000)
Associate Professor
Department of Pediatrics
Mount Sinai School of Medicine
New York, New York

Theresa A. Shapiro, M.D., Ph.D. (2000)
Associate Professor
Department of Medicine, Pharmacology, and Molecular Sciences
School of Medicine
Johns Hopkins University
Baltimore, Maryland

Richard P. Wenzel, M.D. (2001)
Professor and Chair
Department of Internal Medicine
Medical College of Virginia
Virginia Commonwealth University
Richmond, Virginia

Christopher C. Whalen, M.D. (2003)
Associate Professor
Department of Epidemiology and Biostatistics
School of Medicine
Case Western Reserve University
Cleveland, Ohio

Brian Wong, M.D. (2000)
Associate Professor
Department of Internal Medicine
School of Medicine
Yale University
West Haven, Connecticut

Scientific Review Administrator

Gary Madonna, Ph.D.
Microbiology and Infectious Diseases Research Committee
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Bethesda, Maryland

Board of Scientific Counselors

The Board of Scientific Counselors advises the Director, NIH, the Deputy Director for Intramural Research, NIH, the Director, NIAID, and the Director, Division of Intramural Research (DIR), NIAID, concerning the Institute's intramural research programs. The Board's recommendations are based on rigid and objective reviews of NIAID laboratories to assess ongoing research, as well as future directions, and to evaluate the productivity and performance of NIAID's tenured scientists, tenure-track scientists, and the Scientific Director. Following each review, the written report from the Board is forwarded, with a response from the Director, DIR, NIAID, to the Deputy Director for Intramural Research, NIH. In addition, the Board's recommendations are communicated annually to the National Advisory Allergy and Infectious Diseases Council.

The Board's review process strengthens NIAID's tenure system and the overall quality of the Institute's research. As a result of the Board's scientific review, NIAID may modify or redirect its intramural research priorities to allow for scientific growth of investigators as well as pursuit of important new areas of research. Its findings have a direct impact on the allocation of personnel, budget, and space resources within each laboratory.

The Board of Scientific Counselors roster is located at the web site http://www.niaid.nih.gov/facts/bscroste.htm.

Roster

(Terms expire June 30 of the year shown.)

J. Donald Capra, M.D. (2002) (Chair)
President and Scientific Director
Oklahoma Medical Research Foundation
Oklahoma City, Oklahoma

Frances M. Brodsky, D.Phil. (2004)
Professor
Department of Pharmacy and Pharmaceutical Chemistry
Department of Microbiology and Immunology
Hooper Foundation
University of California at San Francisco
San Francisco, California

Charles A. Dinarello, M.D. (2001)
Professor of Medicine
Division of Infectious Diseases
School of Medicine
University of Colorado Health Science Center
Denver, Colorado

Irma Gigli, M.D. (2002)
Professor of Medicine
Institute of Molecular Medicine for the Prevention of Human Diseases
University of Texas Houston Health Science Center at Houston
Houston, Texas

George V. Hillyer, Ph.D. (2004)
Chancellor
University of Puerto Rico, Rio Piedras Campus
San Juan, Puerto Rico

Elliott D. Kieff, M.D., Ph.D. (2003)
Harriet Ryan Albee Professor
Department of Medicine, Microbiology and Molecular Genetics
Channing Laboratory
Brigham and Women's Hospital
Harvard University
Boston, Massachusetts

Robert S. Munford, M.D. (2004)
Jan and Henri Bromberg Chair in Internal Medicine
Professor of Microbiology
Infectious Disease Division
Department of Internal Medicine
University of Texas Southwestern Medical Center
Dallas, Texas

Barbara A. Osborne, Ph.D. (2005)
Professor
Department of Veterinary and Animal Sciences
University of Massachusetts
Amherst, Massachusetts

Richard J. Whitley, M.D. (2004)
Loeb Chair in Pediatrics
Professor of Pediatrics, Microbiology, and Medicine
Department of Pediatrics
Children's Hospital
University of Alabama at Birmingham
Birmingham, Alabama

Executive Secretary

Thomas J. Kindt, Ph.D.
Director
Division of Intramural Research
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Bethesda, Maryland

NIAID Executive Committee

The Executive Committee is the senior internal policy and advisory group to the Director, NIAID, and acts as a forum for discussing and setting important Institute-wide scientific and management policies and for discussing special issues and concerns that affect NIAID programs. As such, the Executive Committee consists of NIAID senior scientific and management staff, as well as several ad hoc members who provide program-staff-level input. All new, expansion, and renewal program initiatives are reviewed by the Executive Committee at the earliest possible stage of project development to provide the NIAID Director and senior staff the opportunity to discuss and consider the merit and relationship of all projects to the ongoing programs of the Institute. The Executive Committee also serves as the vehicle for senior NIAID management to communicate with Institute program staff regarding issues and policies that are being considered for implementation at both the NIAID and NIH levels.

The Executive Committee roster is located at the web site http://www.niaid.nih.gov/facts/executivecom.htm.

Anthony S. Fauci, M.D. (Chair)
Director

John R. La Montagne, Ph.D.
Deputy Director

Lynn C. Hellinger
Associate Director for Management and Operations

Wayne Crum
Acting Director
Office of Financial Management

Mark Dybul, M.D.
Assistant Director for Medical Affairs

Leslie Fink
Director
Office of Communications and Public Liaison

Gregory K. Folkers
Senior Public Affairs Advisor
Officer of the Director

Carole A. Heilman, Ph.D.
Director
Division of Microbiology and Infectious Diseases

Elizabeth Holmes
Acting Director
Office of Human Resources Management

Milton J. Hernandez, Ph.D.
Director
Office of Special Populations and Research Training

Jack Y. Killen, M.D.
Director
Division of Acquired Immunodeficiency Syndrome

Thomas J. Kindt, Ph.D.
Director
Division of Intramural Research

Vacant
Director
Office of Policy Analysis

H. Clifford Lane, M.D.
Director
Office of Clinical Research

John J. McGowan, Ph.D.
Director
Division of Extramural Activities

Gary Nabel, M.D., Ph.D.
Director
Vaccine Research Center

Roger E. Pellis
Executive Officer and Director
Office of Administrative Services

Michael Mowatt, Ph.D.
Acting Director
Office of Technology Development

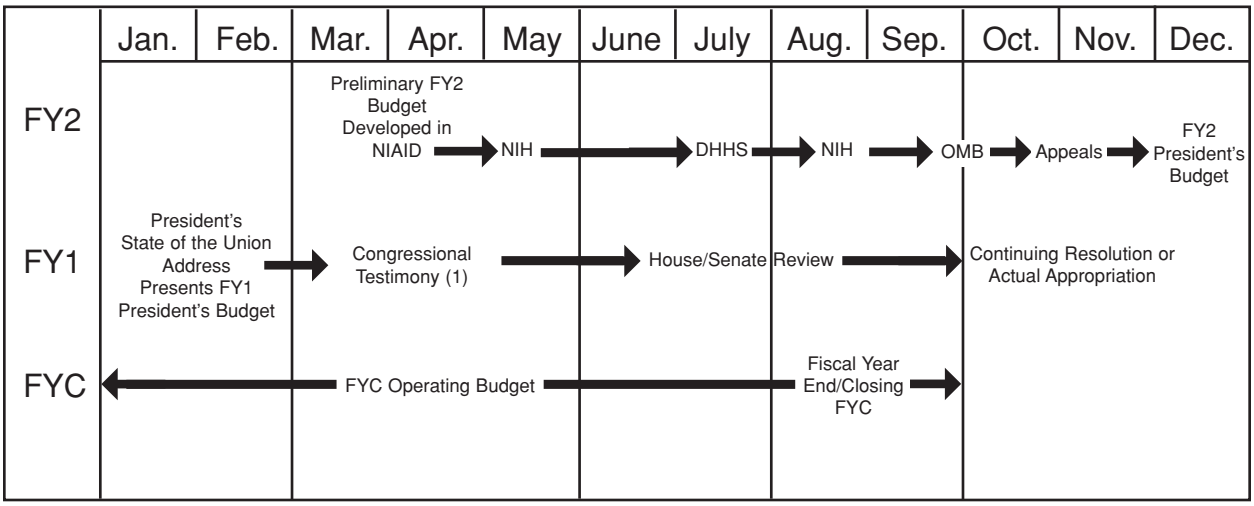
Daniel Rotrosen, M.D.
Director
Division of Allergy, Immunology and Transplantation

Karen Santoro, J.D.
Director
Office of Ethics

Karl A. Western, M.D., D.T.P.H.
Assistant Director for International Research
Office of the Director

Laurence B. Wolfe, Ph.D.
Director
Office of Technology Information Systems

Federal Budget Process

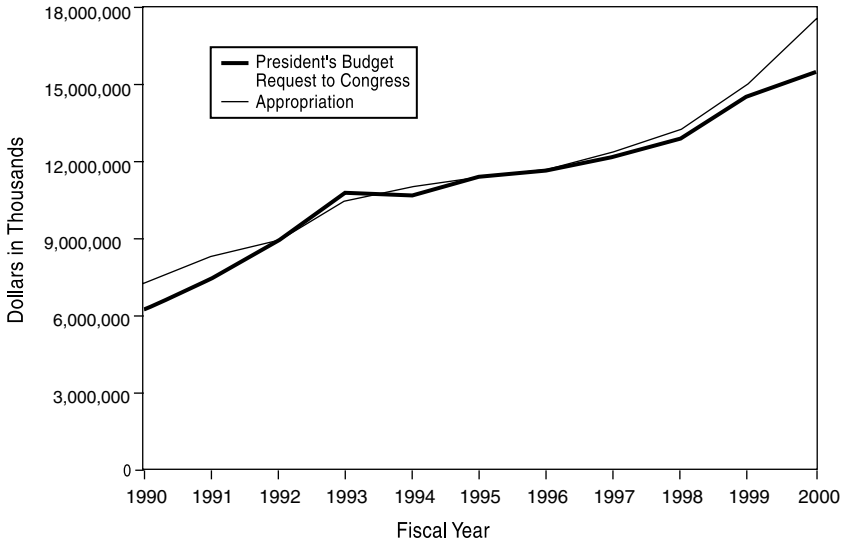


Fiscal year = October 1 to September 30

FY2 = second future fiscal year
FY1 = first future fiscal year
FYC = current fiscal year

(1) NIH Director and NIH IC Directors, including Director, NIAID, provide congressional testimony to the House and Senate Appropriations Subcommittee on Labor, Health, and Human Services and Education.

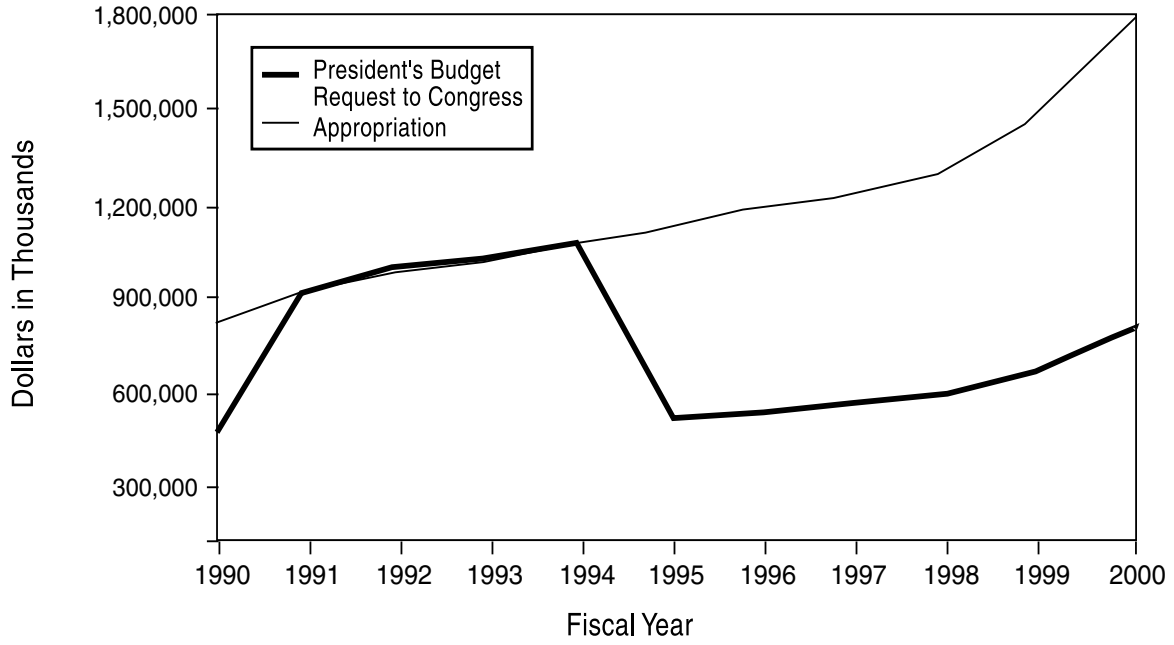
NIH Appropriations History: FY 1990–2000



Fiscal Year	President's Budget Request to Congress	House Allowance	Senate Allowance	Appropriation[a]
		(Dollars in Thousands)		
1990	6,776,727,000 [b]	7,678,625,000 [c]	7,713,064,000 [c]	7,576,352,000 [d]
1991	7,929,686,000	8,317,654,000 [e]	8,347,085,000	8,276,632,000 [f]
1992	8,774,886,000	8,824,886,000	8,978,133,000	8,921,687,000 [g]
1993	10,579,684,000	10,368,551,000	10,387,721,000	10,326,604,000 [h]
1994	10,667,984,000	10,936,652,000	10,956,389,000	10,937,653,000 [i]
1995	11,473,000,000	11,322,023,000	11,333,181,000	11,299,522,000 [j]
1996	11,773,066,000	11,939,001,000	11,639,204,000	11,927,562,000 [k]
1997	12,406,300,000 [l]	12,747,203,000	12,414,580,000 [m]	12,740,843,000 [n]
1998	13,078,203,000 [o]	13,505,294,000	13,692,844,000	13,647,843,000 [p]
1999	14,763,313,000 [q]	14,862,023,000	15,622,385,000	15,612,386,000 [r]
2000	15,932,786,000	16,936,314,000	17,613,470,000	17,826,571,000

[a] Reflects enacted supplementals, rescissions, and reappropriations.
[b] The 1990 request excludes funds for AIDS, proposed for consolidation in the Office of the Assistant Secretary for Health.
[c] Includes $752,670,000 for AIDS research.
[d] Reflects reductions of $10,000,000 for extramural salary cap savings, $4,000,000 for procurement reform, and a $10,428,000 reduction in salaries and expenses; includes sequester of $96,570,000.
[e] Excludes $304,814,000 not considered.
[f] Reflects an enacted administrative reduction of $29,909,000 for salaries and expenses and $205,134,000 associated with the 2.41 percent across-the-board reduction; includes sequester of $107,000.
[g] Reflects an enacted administrative reduction of $69,603,000 for salaries and expenses, a travel reduction of $5,984,000, and a rescission of $13,131,000.
[h] Reflects enacted administrative reductions of an across-the-board 0.8 percent of $83,571,000, $34,857,000 for salaries and expenses, and a consultant services reduction of $1,342,000. All columns adjusted to include transfer from ADAMHA.
[i] Reflects a salaries and expense rescission of $18,120,000. Excludes $1,000,000 supplemental in NCRR for earthquake relief.
[j] Includes $1,299,328,000 for NIH research appropriated to the NIH Office of AIDS Research. Reflects enacted reductions of $7,446,000 for procurement, $345,000 for rent and $4,401,000 for bonus pay, and a rescission of $10,000,000 in NCRR for construction and $12,384,000 in administrative costs.
[k] Includes $1,410,925,000 appropriated to the ICDs for HIV research. Incorporates the NIH share of the Government-wide administrative cost rescission ($5,780,000) and the Labor/HHS/Education bonus pay rescission ($5,659,000).
[l] Includes $1,431,908,000 for HIV research in the NIH Office of AIDS Research.
[m] Includes $1,460,312,000 for HIV research in the NIH Office of AIDS Research.
[n] Includes $1,501,073,000 for HIV research in the NIH Office of AIDS Research. Incorporated the NIH share of the salaries and expenses reduction ($6,140,000) and the public/legislative affairs reduction ($220,000).
[o] Includes $1,540,765,000 for HIV research in the NIH Office of AIDS Research.
[p] Includes $1,607,053,000 appropriated to the ICs for HIV research.
[q] Reflects a decrease of $34,530,000 for the budget amendment for bioterrorism. Includes $1,728,099,000 for HIV research in the NIH Office of AIDS Research.
[r] Includes $1,798,424,000 appropriated to the ICs for HIV research.

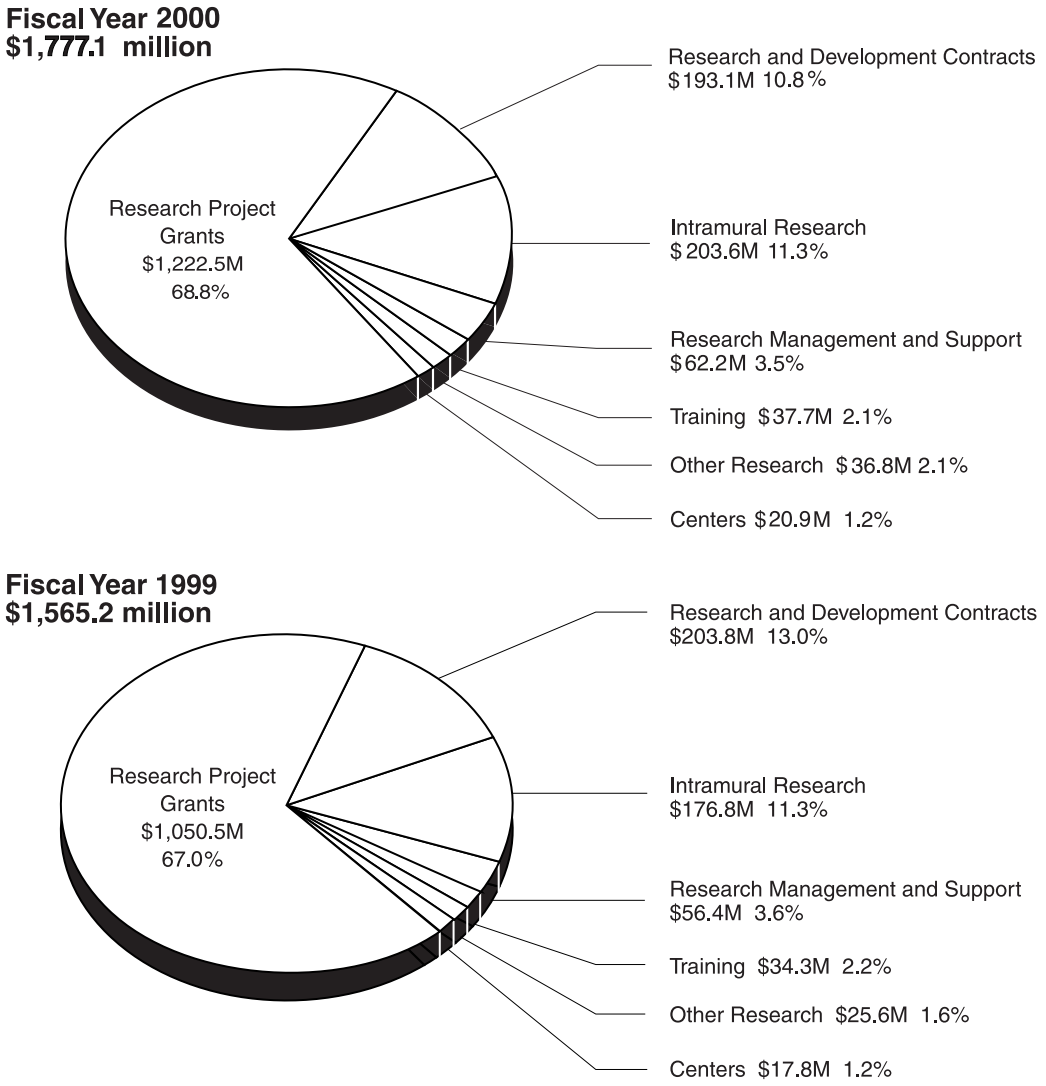
NIAID Appropriations History: FY 1990–2000



Fiscal Year	President's Budget Request to Congress	House Allowance	Senate Allowance	Appropriation[a]
		(Dollars in Thousands)		
1990	442,596 [b]	845,523	847,112	832,977 [c]
1991	886,875	944,965	904,010	906,239 [d]
1992	976,711	972,830	965,952	959,914 [e]
1993	1,010,845	990,055	989,055	979,471 [f]
1994	1,065,583	1,065,583	1,065,583	1,063,704 [g]
1995	542,864 [h]	1,094,633	1,094,633	1,092,507 [i]
1996	557,354 [h]	1,169,628	1,139,326	1,171,168 [j]
1997	584,362 [h]	1,256,149	1,229,009	1,257,794 [k]
1998	634,272 [h]	1,339,459	1,359,688	1,352,119 [l]
1999	703,723 [h,m]	1,470,460	1,540,102	1,569,063
2000	789,156	1,694,019	1,786,718	1,797,988 [n]

[a] Reflects enacted supplementals, rescissions, and reappropriations.
[b] Excludes funds for the national HIV program ($400,116,000) proposed for consolidation in the Office of the Assistant Secretary for Health.
[c] Excludes an enacted administrative reduction of $2,573,000; includes sequester of $10,768,000.
[d] Excludes an enacted administrative reduction of $26,986,000; includes sequester of $12,000.
[e] Excludes an enacted administrative reduction of $11,197,000.
[f] Excludes an enacted administrative reduction of $12,334,000.
[g] Includes rescission of $1,879,000.
[h] Excludes funds for HIV research activities consolidated in the NIH Office of AIDS Research.
[i] Includes a rescission of $1,293,000 and a transfer of $458,000.
[j] Includes an enacted administrative reduction of $1,145,000 and a net NIH Director's transfer of $2,685.
[k] Includes a rescission of $575,000 for administrative expenses and a net positive transfer of $1,135,000 from the NIH Director's Reserve.
[l] Includes rescissions and transfers.
[m] Reflects an increase of $1,683,000 for the budget amendment for bioterrorism.
[n] Includes a rescission amount of $5,075.

NIAID Funding by Budget Mechanism: FY 1999–2000



Budget Mechanism	FY 2000[a]	% of Total	FY 1999[a]	% of Total	% Change
Research Project Grants					
Noncompeting	$775,572		$730,504		
Competing	446,988		319,998		
Subtotal, RPGs	1,222,560	68.8	1,050,502	67.0	+16.4
Centers	20,932	1.2	17,798	1.2	+17.6
Other Research	36,839	2.1	25,550	1.6	+44.2
Training	37,744	2.1	34,269	2.2	+10.1
R&D Contracts	193,192	10.9	203,804	13.0	-5.5
Subtotal, Extramural	1,511,267		1,331,923		+13.5
Intramural Research	203,656	11.5	176,846	11.3	+15.2
Research Management and Supp.	62,231	3.5	56,432	3.6	+10.3
Total	**$1,777,154**		**$1,565,201**		**+13.5**

[a] Dollars in thousands and reflects “actuals” versus appropriations.

NIAID Funding by the FY 2000 NIH Plan for HIV-Related Research[a] (Dollars in Thousands)

	FY 1999 Actual		FY 2000 Actual	
	Amount	Percent of Total	Amount	Percent of Total
I. Natural History and Epidemiology	110,672	13.8	116,925	12.8
Change from Prior Fiscal Year			*5.7%*	
II. Etiology and Pathogenesis	226,966	28.4	250,127	27.3
Change from Prior Fiscal Year			*10.2%*	
III. Therapeutics	274,753	34.3	317,077	34.6
Change from Prior Fiscal Year			*15.4%*	
IV. Vaccines	135,771	17.0	173,143	18.9
Change from Prior Fiscal Year			*27.5%*	
V. Behavioral Research	12,907	1.6	15,482	1.7
Change from Prior Fiscal Year			*20.0%*	
VI. Training and Infrastructure	28,106	3.5	30,467	3.3
Change from Prior Fiscal Year			*8.4%*	
VII. Information Dissemination	11,210	1.4	12,509	1.4
Change from Prior Fiscal Year			*11.6%*	
Total Funding by the FY 2000 Plan	800,385	100.0	915,730	100.0
Change from Prior Fiscal Year			*14.4%*	

[a] A comprehensive plan for HIV-related research developed by the NIH Office of AIDS Research and the NIH Institutes and Centers.

Legislative Chronology

November 1, 1948—The National Microbiological Institute was established under authority of section 202 of the Public Health Service Act, as implemented by General Circular No. 55, Organization Order No. 20, dated October 8, 1948.

December 29, 1955—NIAID was established (replacing the National Microbiological Institute) under authority of the Omnibus Medical Research Act (P.L. 81-692, 64 Stat. L. 443), as implemented by a Public Health Service Briefing Memorandum of November 4, 1955, from the Surgeon General to the Secretary of Health, Education, and Welfare.

November 4, 1988—NIAID was provided with additional authorities for AIDS research under Title II of the Health Omnibus Programs Extension (HOPE legislation) of 1988 (P.L. 100-607), the first major law to address AIDS research, information, education, and prevention.

August 14, 1991—The Public Health Service Act was amended by Public Law 102-96, the "Terry Beirn Community-Based AIDS Research Initiative Act of 1991," which reauthorized NIAID's Community Programs for Clinical Research on AIDS (CPCRA).

CPCRA was renamed in honor of Mr. Beirn (an AIDS activist and congressional staffer who died in 1991) and was reauthorized for an additional 5 years.

June 10, 1993—The Public Health Service Act was amended by Public Law 103-43, the National Institutes of Health Revitalization Act of 1993. This comprehensive legislation required NIAID to include research on tropical diseases in its mission statement and directs the Secretary, U.S. Department of Health and Human Services, to ensure that individuals with expertise in chronic fatigue syndrome or neuromuscular diseases are appointed to appropriate NIH advisory committees.

December 14, 1993—The Preventive Health Amendments of 1993 were passed, which included provisions requiring the Director, NIAID, to conduct or support research and research training regarding the cause, early detection, prevention, and treatment of tuberculosis. (The Institute already had authority to conduct such research under its authorities in Title IV, Public Health Service Act.)

November 29, 1999—The FY 2000 Appropriations Act (P.L. 106-113) established the NIH Challenge Grants program to promote joint ventures between the NIH and the biotechnology, pharmaceutical, and medical device industries. A one-time funding level of $20 million was provided within the Public Health and Social Services Emergency Fund.

October 17, 2000—The Children's Health Act (P.L. 106-310) required the NIAID and NIAMS Directors to expand and intensify the activities of their Institutes with respect to research and related activities concerning juvenile arthritis and related conditions.

November 13, 2000—The Public Health Improvement Act (P.L. 106-505) authorized the NIAID Director to establish a program of clinical research and training awards for sexually transmitted diseases.

Previous Directors

Victor H. Haas, M.D., 1948-1957
Justin M. Andrews, Sc.D., 1957-1964
Dorland J. Davis, M.D., D.P.H., 1964-1975
Richard M. Krause, M.D., 1975-1984

NIAID-Supported Repositories

NIAID's intramural and extramural researchers have developed an ample supply of resources and reagents that are used by scientists worldwide for basic research, applied research to develop therapeutics and vaccines, and commercialization. These resources include peptides, cell lines, monoclonal antibodies, viral vectors, and animal models.

Division of Acquired Immunodeficiency Syndrome

Biological Reagents and Reference Standards

The AIDS Research and Reference Reagent Program acquires and distributes state-of-the-art reagents for AIDS-related research and makes these reagents available to qualified investigators throughout the world. It also encourages and facilitates technology transfer through publication of methods and provision of standardized panels and protocols, facilitates commercial development of reagents, and participates as an AIDS Collaborating Center of the World Health Organization (WHO). For more information, see http://www.niaid.nih.gov/aidsvaccine/nihreagent.htm.

Human HIV Specimens

Research on HIV transmission and disease progression patterns greatly benefits from a centralized system for receiving, cataloging, storing, and distributing samples collected from various well-characterized cohorts of HIV-infected individuals. NIAID provides state-of-the-art storage and computerized inventory management of specimens from domestic and international HIV epidemiology studies, HIV therapeutic and vaccine trials, and other prevention research studies through its central repositories. By making these specimens available to the scientific community, the Division of Acquired Immunodeficiency Syndrome fosters collaboration among scientific investigators to promote further progress in the detection, treatment, and prevention of HIV disease.

Division of Allergy, Immunology and Transplantation

Congenic Non-Obese Diabetic Mice Strains

NIAID investigators, in collaboration with Merck Laboratories, produced a series of congenic strains of the non-obese diabetic (NOD) mouse, a model of spontaneous type 1 diabetes. As Merck Laboratories closes its NOD mouse research program, NIAID, the Juvenile Diabetes Research Foundation International, and the Wellcome Trust are collaborating with Merck Genome Research Institute to transfer these unique animals to Taconic Farms, Incorporated, to ensure that they will remain available to the research community. Several of the strains show susceptibility for other autoimmune diseases, specifically experimental autoimmune encephalomyelitis.

Multiple Autoimmune Disease Genetics Consortium (MADGC)

The research resource, MADGC, is a repository of genetic and clinical data and materials collected from 400 families in which at least three individuals are affected by at least two autoimmune diseases. The central registry of families is located at North Shore University Hospital, with the University of Minnesota-Twin Cities and the University of

California-San Francisco collaborating in the collection effort. The research materials will be used for studies to identify and characterize genes involved in the susceptibility or resistance to developing autoimmune diseases. For more information, see www.madgc.org.

NIAID Tetramer Facility

The NIAID Tetramer Facility, supported by the Division of Allergy, Immunology and Transplantation (DAIT), the Division of Microbiology and Infectious Diseases (DMID), the Division of Acquired Immunodeficiency Syndrome (DAIDS), the Division of Intramural Research (DIR), and the National Cancer Institute, produces peptide-major histocompatibility complex reagents for T-cell detection and has provided more than 500 tetramers to investigators in its first 18 months of operation. Reagents are provided for the study of T-cell responses relevant to vaccine research and development for many diseases, including intracellular bacterial, viral, and parasite infections and autoimmune diseases. Information on the NIAID Tetramer Facility can be found at http://www.niaid.nih.gov/reposit/tetramer/index.html.

NIH Autoimmune Rat Model Repository and Development Center

The NIH Autoimmune Rat Model Repository and Development Center is a central resource for the development of rat models of autoimmune disorders, which are available to researchers upon request. This program is a collaborative effort among NIAID, the National Institute of Arthritis and Musculoskeletal Diseases (NIAMS), and the NIH Office of Research Services' Veterinary Resources Program. For more information, see http://www.ors.od.nih.gov/dirs/vrp/ratcenter.

North American Rheumatoid Arthritis Consortium (NARAC)

NARAC is a repository of genetic and clinical materials from more than 700 families in which at least two siblings are afflicted with rheumatoid arthritis. The central repository is located at North Shore University Hospital. Clinical data and materials are available to researchers for genetic studies on susceptibility to rheumatoid arthritis. NIAID, NIAMS, and the Arthritis Foundation cofund this resource. For more information, see http://128.218.179.215/medicine/rheum/narac/nfnarac.htm.

Primary Immunodeficiency Disease Registry

NIAID, through a contract with the Immune Deficiency Foundation (IDF), maintains a registry of clinical information on U.S. residents affected by primary immunodeficiency diseases. For each disease, the registry collects information on incidence; clinical phenotypes and phenotype/genotype correlations; natural course of the disease, including early and late complications; effects of therapy; causes of death; and prognosis. Investigators may apply to the registry to obtain access to physicians with these unique patients for both basic studies and clinical trials. In addition, affected individuals have access to the latest information and therapies. The diseases included in the registry are chronic granulomatous disease, hyper-IgM syndrome, severe combined immunodeficiency disease (SCID), X-linked agammaglobulinemia, Wiskott-Aldrich syndrome, common variable immunodeficiency, leukocyte adhesion deficiency, and DiGeorge syndrome.

Division of Intramural Research

Transgenic and Gene-Targeted Mice Repository

NIAID's Division of Intramural Research, in collaboration with the Division of Allergy, Immunology and Transplantation, supports facilities for the acquisition, breeding, and distribution of transgenic and gene-targeted (knockout) mice, which are mice that are genetically engineered to serve as animal models for human diseases that do not occur in nonhuman species. The repository provides these mice to both intramural and extramural investigators through the NIAID/Taconic exchange for use in research and for development of clinical therapies in various infectious and immunologic diseases.

Division of Microbiology and Infectious Diseases

Leprosy Research Support and Armadillo Colony Maintenance

Although the prevalence of leprosy has declined significantly because of multidrug therapy, leprosy remains a problem worldwide. A major obstacle to leprosy research, however, is the difficulty in culturing *Mycobacterium leprae*, the organism responsible for leprosy. To overcome this problem, the Division of Microbiology and Infectious Diseases (DMID) supports the maintenance of an armadillo colony, the best animal model system of *M. leprae* infection. DMID also funds a repository of viable *M. leprae* and purified, defined reagents derived from *M. leprae*, which are available to researchers worldwide. For more information, see http://www.cvmbs.colostate.edu/microbiology/leprosy.

Parasitic Disease Research Support

DMID supports three research repositories that supply parasitic organisms whose life cycles are typically too costly or too difficult for investigators to maintain in their own laboratories.

Schistosomiasis and Filariasis Research Repositories. The schistosomiasis repository provides qualified requesters with rodent-definitive hosts and with snail intermediate hosts infected with *Schistosoma mansoni, S. japonicum*, and *S. haematobium*. The filariasis repository provides rodent-definitive hosts and mosquito intermediate hosts infected with *Brugia malayi, B. pahangi*, or *Dirofilaria immitis*. Organisms are provided free of charge, except for shipping costs, to both NIH-supported and independent investigators.

Malaria Research and Reference Reagent Resource Center. The malaria resource center has been established to acquire, produce, and distribute malaria research reagents, reference materials, and other information to qualified investigators throughout the world. A major component of the program is the quality control of reagents, standardization of protocols, and exploration of new technologies. International workshops and training sessions will be organized to stimulate and support both laboratory-based and field-based research. The long-term goal of the resource center is to promote technology transfer as well as to facilitate research leading to commercial development of reagents for malaria diagnostics, prevention, and treatment. For more information, see http://www.malaria.mr4org/mr4pages/index.html.

Pneumococcal Reference Laboratory

This laboratory provides reference and resource services and expertise to facilitate the evaluation of improved pneumococcal vaccine. A major objective is to establish a consensus assay and to improve and modify procedures for measuring antibody activity to pneumococci. It also provides radiolabeled polyribosylribose phosphate (PRP) and/or suitably derivatized PRP and purified PRP to laboratories for the performance of *Haemophilus influenzae* type b assays and for calibration of immunodiagnostic assays.

Repository for Biological Reagents and Reference Standards

This repository stores and distributes serological and microbiological reagents for use as reference standards and for research in infectious and immunologic diseases. As a WHO Collaborating Center for Antiviral Drugs and Interferon, the NIAID Repository is responsible for the storage and worldwide distribution of WHO International Interferon Standards and Reference Reagents.

Tuberculosis Research Materials and Vaccine Testing

Mycobacterium tuberculosis, the organism responsible for tuberculosis (TB), is difficult and time-consuming to grow and, because it is transmitted via aerosols, should be studied only in appropriate biohazard facilities. DMID funds a repository to provide *M. tuberculosis*-derived materials to qualified TB investigators worldwide in basic and clinical research areas, allowing work to begin quickly and eliminating the need for these investigators to have their own biohazard facilities. DMID also funds the screening, in established, small-animal, low-dose, aerosol-challenge models, of potential anti-tuberculosis vaccine candidates provided by individual researchers. For more information, see http://www.cvmbs.colostate.edu/microbiology/tb/top.htm.

NIH Extramural Funding Mechanisms Used by NIAID

D43 International Training Grant in Epidemiology—improves and expands epidemiologic research and the utilization of epidemiology in clinical trials and prevention research in foreign countries through support of training programs for foreign health professionals, technicians, and other health care workers.

F31 Predoctoral Individual National Research Service Award (NRSA)—provides predoctoral individuals with supervised research training in specified health and health-related areas leading toward the research degree (e.g., Ph.D.).

F32 Postdoctoral Individual National Research Service Award (NRSA)—provides postdoctoral research training to individuals to broaden their scientific background and extend their potential for research in specified health-related areas.

F33 National Research Service Award for Senior Fellows (NRSA)—provides opportunities for experienced scientists to make major changes in the direction of their research careers, to broaden their scientific background, or to acquire new research capabilities.

F35 Intramural NRSA Individual Postdoctoral Program—supports a postdoctoral trainee in the NIH intramural program.

G12 Research Centers in Minority Institutions (RCMI) Award—assists predominantly minority institutions that offer a doctorate in the health professions of health-related sciences to strengthen and augment their human and physical resources for the conduct of biomedical research. (Awards are administered by the National Center for Research Resources [NCRR].)

K01 Research Scientist Development Award—Research and Training—supports scientists, committed to research, in need of both advanced research training and additional experience.

K02 Independent Scientist Award—provides support for newly independent scientists who can demonstrate the need for a period of intensive research focus as a means of enhancing their research careers.

K04 Modified Research Career Development Award—fosters the development of young scientists with outstanding research potential for careers in independent research in the health-related sciences.

K06 Research Career Award—enables institutions to finance positions favorable to the intellectual growth and research productivity of established, highly competent investigators for the duration of their careers. (Funding for new K06s was discontinued in 1996.)

K08 Clinical Investigator Award—provides the opportunity for promising medical scientists (with demonstrated aptitude to develop into independent investigators) or faculty members who

will pursue research aspects of categorical areas applicable to the awarding unit, and aids in filling the important academic faculty gap in these shortage areas within health professional institutions of the country.

K11 Physician Scientist Award (individual)—supports a newly trained clinician, nominated by an institution, for the development of independent research skills and experience in a fundamental science.

K22 Career Transition Award—provides support to outstanding newly trained basic or clinical investigators to develop their independent research skills through a two-phase program: an initial period involving an intramural appointment of the NIH and a final period of support at an extramural institution. The award is intended to facilitate the establishment of a record of independent research by the investigator to sustain or promote a successful research career.

K23 Mentored Patient-Oriented Research Career Development Award—provides support for the career development of investigators who have made a commitment to focus their research endeavors on patient-oriented research. This mechanism provides support for a 3-year minimum up to a 5-year period of supervised study and research for clinically trained professionals who have the potential to develop into productive clinical investigators.

K24 Midcareer Investigator Award in Patient-Oriented Research—provides support for experienced clinicians to allow them protected time to devote to patient-oriented research and to act as mentors for beginning clinical investigators.

K30 Clinical Research Curriculum Award (CRCA)—The CRCA is an award to institutions and is intended to stimulate the inclusion of high-quality, multidisciplinary didactic training as part of the career development of clinical investigators. This award is intended to support the development of new didactic programs in clinical research at institutions that do not currently offer such programs or in institutions with existing didactic programs in clinical research to support or expand their programs or to improve the quality of instruction.

N01 Research and Development Contract—develops or applies new knowledge or tests, screens, or evaluates a product, material, device, or component for use by the scientific community.

N43 Small Business Innovation Research
N44 (SBIR) Contracts—enable small businesses possessing technological expertise to contribute to the R&D mission of the NIH. Phase I (N43) contracts support projects, limited in time and amount, to establish the technical merit and feasibility of R&D ideas that may ultimately lead to commercial products or services. Phase II (N44) contracts support in-depth development of R&D ideas for which

feasibility has been established in phase I and that are likely to result in commercial products or services.

P01 Research Program Project—provides a qualified institution on behalf of a principal investigator with the support of a broadly based, multidisciplinary, often long-term research program with a particular major objective or theme. A program project involves the organized efforts of groups of investigators who conduct research projects related to the overall program objective. The grant can provide support for the projects and for certain shared resources necessary for the total research effort. Each project supported under a program project grant is expected to contribute to the overall program objective.

P30 Center Core Grant—supports shared resources and facilities for categorical research by a number of investigators from different disciplines who prove a multidisciplinary approach to a joint research effort or from the same discipline who focus on a common research problem. Although funded independently of the center's component projects or program projects, the core grant relates integratively to them. By providing more accessible resources, this support is expected to ensure greater productivity than that obtained from the separate projects and program projects.

P41 Biotechnology Resource Grants—support biotechnology resources available to all qualified investigators without regard to the scientific disciplines or disease orientations of their research activities or specifically directed to a categorical program area.

P50 Specialized Center—supports any part of the full range of R&D, from basic to clinical, and may involve ancillary supportive activities such as protracted patient care necessary to the primary research or R&D effort. The spectrum of activities comprises a multi-disciplinary attack on a specific disease entity or biomedical problem area. These grants differ from program project grants in that they are usually developed in response to an announcement of the programmatic needs of an Institute or Division and subsequently receive continuous attention from its staff. Centers also may serve as regional or national resources for special research purposes.

R01 Research Project Grant (traditional)—provides support to an institution (domestic or foreign) on behalf of a principal investigator for a discrete project related to the investigator's interests and competence. Most of the research that the NIH supports is maintained through this support mechanism. Although rare, such a grant may be awarded directly to an individual.

R03 Small Grant—provides research support specifically limited in time and amount for studies in categorical program areas. Small grants provide flexibility for initiating studies, which

are generally for preliminary short-term projects and are nonrenewable.

R13 Conference Grant—provides funding for conferences to coordinate, exchange, and disseminate information related to program interests. Generally, such awards are modest and limited to participation with other organizations in the support of conferences rather than as a provision of sole support. Among the costs eligible for support are salaries, equipment rental, travel, consultant services, and supplies. Prospective applicants should inquire in advance concerning possible interest on the part of an Institute.

R15 Academic Research Enhancement Award (AREA)—provides support to scientists at eligible domestic institutions for small-scale, new, or expanded health-related research projects such as pilot research projects and feasibility studies; development, testing, and refinement of research techniques; secondary analysis of available data sets; and similar discrete research projects that demonstrate research capability. This award is directed toward smaller, less-prominent 4-year public and private colleges and universities that provide undergraduate training for a significant number of U.S. research scientists but have not had an adequate share in the growth of the NIH extramural program.

R18 Research Demonstration and Dissemination Project—provides support to develop, test, and evaluate health-service activities and to foster the application of existing knowledge for the control of categorical diseases.

R21 Exploratory/Developmental Grant—NIAID uses this mechanism for Bridge awards. The Bridge award provides support for limited time and amount to investigators to enable them to continue meritorious research and improve the competitiveness of future grant applications.

R24 Resource-Related Research Project—supports research projects that will enhance the capability of resources to serve biomedical research.

R25 Education Project—provides support to develop and/or implement a program as it relates to category in one or more of the areas of education, information, training, technical assistance, coordination, or evaluation.

R29 First Independent Research Support and Transition (FIRST) Award—supports the first independent investigative efforts of an individual and helps to effect the transition toward the traditional types of NIH research project grants. The sponsoring institution must be a domestic institution. Support generally is for 5 years. (Funding for new R27s was discontinued as of the June 1998 Council for new applications.)

R37 Method to Extend Research in Time (MERIT) Award—provides long-term, stable support to investigators who are likely to continue to perform in an outstanding manner and spares them

the administrative burdens associated with preparing and submitting research grant applications. An initial 5-year award is accompanied by an opportunity for a 3-year to 5-year extension, based on an expedited review of the accomplishments during the initial award period. Investigators may not apply for a MERIT award. NIH staff and advisors base their selection of MERIT award recipients on competing R01 applications, prepared and submitted in accordance with NIH procedures. MERIT awards are awarded to a limited number of selected investigators who have demonstrated superior competence and outstanding productivity during previous research endeavors.

R41 Small Business Technology Transfer
R42 (STTR) Grants—support cooperative R&D projects between small business concerns and research institutions, limited in time and amount, to establish the technical merit and feasibility of ideas that have potential for commercialization. Awards are made to small business concerns only.

R43 Small Business Innovation Research
R44 (SBIR) Grants—enable small businesses possessing technological expertise to contribute to the R&D mission of the NIH. Phase I (R43) grants support projects, limited in time and amount, to establish the technical merit and feasibility of R&D ideas that ultimately may lead to commercial products or services. Phase II (R44) grants support in-depth development of R&D ideas whose feasibility has been established in phase I and that are likely to result in commercial products or services. The research must be conducted in the United States.

S06 Minority Biomedical Research Support (MBRS) Program—strengthens the biomedical research and research training capability of ethnic minority institutions, and thus establishes a more favorable milieu for increasing the involvement of minority faculty and students in biomedical research. Awards are administered by the National Institute of General Medical Sciences [NIGMS].

T32 Institutional National Research Service Award (NRSA)—enables institutions to grant NRSAs for predoctoral and postdoctoral research training in specified shortage areas to individuals selected by the institutions.

T35 NRSA Short-Term Research Training—provides individuals with research training during off-quarters or summer periods to encourage research careers or research in areas of national need.

T36 Minority Access to Research Careers (MARC) Ancillary Training Activity—increases the number of well-trained minority scientists in biomedical disciplines and strengthens the research and teaching capabilities of minority institutions through a variety of training mechanisms. These include visits by experienced scientists to minority institutions or workshops/ conferences designed to enhance the

research training experience of students and faculty from minority institutions. (Awards are administered by NIGMS.)

U01 Research Project (Cooperative Agreement)—provides an assistance relationship between the NIH and a recipient, but with substantial programmatic involvement by the NIH. The NIH assists, supports, or stimulates the recipients and is involved substantially with recipients in conducting projects similar in program content to those for grants, with the NIH playing a "partner" role in the effort.

U09 Scientific Review and Evaluation (Cooperative Agreement)—provides the chairperson of an Initial Review Group with administrative funds for operation of the review group.

U19 Research Program (Cooperative Agreements)—supports a research program of multiple projects directed toward a specific major objective, basic theme, or program goal, requiring a broadly based, multidisciplinary, and often long-term approach.

U24 Resource-Related Research Projects/Cooperative Agreements—support research projects contributing to improvement of the capability of resources to serve biomedical research.

U42 Animal (Mammalian and Nonmammalian) Model, and Animal and Biomedical Materials Resource Cooperative Agreements (NCRR)—develop and support an animal (mammalian and nonmammalian) model, or animal or biological materials resources available to all qualified investigators without regard to the scientific disciplines or disease orientations of their research activities or specifically directed to a categorical program. Nonmammalian resources include nonmammalian vertebrates, invertebrates, cell systems, and nonbiological systems.

Y01 NIH Interagency Agreement—provides a written reimbursable agreement by which a component of the NIH provides a source of funds to another Federal organization outside DHHS to acquire specific products, services, or studies.

Y02 NIH Interagency Agreement—provides a written reimbursable agreement by which a component of the NIH provides funds to another NIH component or to another organization within DHHS to acquire specific products, services, or studies.

Acronyms

AACTG	Adult AIDS Clinical Trials Group
ABC	Assistance in Building Capacity (FIC)
ACE	Autoimmunity Centers of Excellence
ACTG	AIDS Clinical Trials Group
ADMO	Associate Director for Management and Operations
AHP	American Home Products Corporation
AIDS	acquired immunodeficiency syndrome
AREA	Academic Research Enhancement Award
ART	antiretroviral therapy
AVEG	AIDS Vaccine Evaluation Group
AVEU	AIDS Vaccine Evaluation Unit
AVRC	AIDS Vaccine Research Committee
AZT	zidovudine
BAMBU	Bacteriology and Mycology Biostatistical Unit
BAMSG	Bacteriology and Mycology Study Group
BMLA	Biological Material License Agreements
BSE	bovine spongiform encephalopathy
BTEP	BioTechnology Engagement Program
CASG	Collaborative Antiviral Study Group
CATG	Collaborative Antiviral Testing Group
CCTAT	Cooperative Clinical Trial in Adult Kidney Transplantation
CCTPT	Cooperative Clinical Trial in Pediatric Kidney Transplantation
CDA	Confidential Disclosure Agreement
CDC	Centers for Disease Control and Prevention
CEL	Commercial Evaluation License
CFS	chronic fatigue syndrome
CGD	chronic granulomatous disease
cGMP	**c**urrent **G**ood **M**anufacturing **P**ractices
CJD	Creutzfeldt-Jacob disease
CMB	Contract Management Branch
CMV	cytomegalovirus
CPCRA	Terry Beirn Community Programs for Clinical Research on AIDS
CRADA	Cooperative Research and Development Agreement
CRC	Cooperative Research Center
CRCA	Clinical Research Curriculum Award
CTA	Clinical Trial Agreement
CTL	cytotoxic T lymphocyte
CTU	Clinical Trials Unit
CWD	chronic wasting disease
DAIDS	Division of Acquired Immunodeficiency Syndrome, NIAID
DAIT	Division of Allergy, Immunology and Transplantation, NIAID
DEA	Division of Extramural Activities, NIAID

DHHS	U.S. Department of Health and Human Services
DIR	Division of Intramural Research, NIAID
DMID	Division of Microbiology and Infectious Diseases, NIAID
DNA	deoxyribonucleic acid
DSA	Drug Screening Agreement
EIR	Employee Invention Report
EPRU	Enteric Pathogens Research Unit
FDA	Food and Drug Administration
FIC	Fogarty International Center
FIRST	First Independent Research Support and Transition Award
FY	fiscal year
GAVI	Global Alliance for Vaccines and Immunization
GP	glycoprotein
HAART	highly active antiretroviral therapy
HBV	hepatitis B virus
HCV	hepatitis C virus
HEV	hepatitis E virus
HIB	*Haemophilus influenzae* type b
HIV	human immunodeficiency virus
HIVNET	HIV Network for Prevention Trials
HLA	human leukocyte antigen
HOPE	Health Omnibus Programs Extension legislation
HPTN	HIV Prevention Trials Network
HPV	human papillomavirus
HSV	herpes simplex virus
HVDDT	HIV Vaccine Design and Development Teams
HVTN	HIV Vaccine Trials Network
IBRP	Introduction to Biomedical Research Program
ICAS	Inner-City Asthma Study
ICIDR	International Collaboration in Infectious Disease Research
ICs	Institutes and Centers
ICTDR	International Centers for Tropical Disease Research
ICU	intensive care unit
IDF	Immune Deficiency Foundation
IHWG	International Histocompatibility Working Group
IL	interleukin
IOM	Institute of Medicine
IPCP	Integrated Preclinical/Clinical Development Program
ITN	Immune Tolerance Network
JDRF	Juvenile Diabetes Research Foundation International

LCI	Laboratory of Clinical Investigation
LPD	Laboratory of Parasitic Diseases
MADGC	Multiple Autoimmune Disease Genetics Consortium
MARC	Minority Access to Research Careers Program
MBRS	Minority Biomedical Research Support Program
M-CRADA	Materials-Cooperative Research and Development Agreement
MDR-TB	multi-drug-resistant tuberculosis
MERIT	Method to Extend Research in Time Award
MHC	major histocompatibility complex
MIM	Multilateral Initiative on Malaria
MOU	Memorandum of Understanding
MRSA	methicillin-resistant *Staphylococcus aureus*
MRTC	Malaria Research and Training Center
MRU	Mycology Research Unit
MSG	Mycoses Study Group
MTA	Material Transfer Agreement
MVDU	Malaria Vaccine Development Unit
MVI	Malaria Vaccine Initiative
NAAID	National Advisory Allergy and Infectious Diseases Council
NARAC	North American Rheumatoid Arthritis Consortium
NARSA	Network on Antimicrobial Resistance in *Staphylococcus aureus*
NASA	National Aeronautics and Space Administration
NCBI	National Center for Biotechnology Information
NCI	National Cancer Institute
NCICAS	National Cooperative Inner-City Asthma Study
NCRR	National Center for Research Resources
NEI	National Eye Institute
NHGRI	National Human Genome Research Institute
NHLBI	National Heart, Lung, and Blood Institute
NHPTTCSG	Non-Human Primate Transplantation Tolerance Cooperative Study Group
NIA	National Institute on Aging
NIAAA	National Institute on Alcohol Abuse and Alcoholism
NIAID	National Institute of Allergy and Infectious Diseases
NIAMS	National Institute of Arthritis and Musculoskeletal and Skin Diseases
NICHD	National Institute of Child Health and Human Development
NIDA	National Institute on Drug Abuse
NIDCD	National Institute on Deafness and Other Communication Disorders
NIDCR	National Institute of Dental and Craniofacial Research
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NIEHS	National Institute of Environmental Health Sciences
NIGMS	National Institute of General Medical Sciences
NIH	National Institutes of Health
NIMH	National Institute of Mental Health

NINDS	National Institute of Neurological Disorders and Stroke
NINR	National Institute of Nursing Research
NIS	Newly Independent States
NLM	National Library of Medicine, NIH
NOD	non-obese diabetic
NRSA	National Research Service Award
NVP	nevirapine
NVPO	National Vaccine Program Office
OARAC	Office of AIDS Research Advisory Council
OAS	Office of Administrative Services, NIAID
OCPL	Office of Communications and Public Liaison, NIAID
OCR	Office of Clinical Research, NIAID
OD	Office of the Director, NIAID
OE	Office of Ethics, NIAID
OEO	Office of Equal Employment Opportunity, NIAID
OFM	Office of Financial Management, NIAID
OHRM	Office of Human Resources Management, NIAID
OI	opportunistic infection
OIRH	Office of International and Refugee Health, DHHS
OPA	Office of Policy Analysis, NIAID
ORWH	Office of Research on Women's Health, NIH
OSPRT	Office of Special Populations and Research Training, NIAID
OTD	Office of Technology Development, NIAID
OTIS	Office of Technology Information Systems, NIAID
OTT	Office of Technology Transfer, NIH
PA	program announcement
PACTG	Pediatric AIDS Clinical Trials Group
PAHO	Pan American Health Organization
PATH	Program for Appropriate Technology in Health
PID	pelvic inflammatory disease
PIV	parainfluenza virus
PLA	Patent License Agreement
PMC	Pasteur Merieux Connaught
PR	protease
PRP	polyribosylribose phosphate
R&D	research and development
RCMI	Research Centers in Minority Institutions
RFA	request for application
RML	Rocky Mountain Laboratories
ROMIS	Research on Molecular Immunology of STDs
RPAB	Referral and Program Analysis Branch, DEA, NIAID
RSV	respiratory syncytial virus

RT	reverse transcriptase
RTI	Research Triangle Institute
SAIC	Science Applications International Corporation
SBIR	Small Business Innovation Research
SBTT	Small Business Technology Transfer
SCID	severe combined immunodeficiency disease
SHIV	simian human immunodeficiency virus
SIV	simian immunodeficiency virus
SLA	Simple Letter Agreement
SLE	systemic lupus erythematosus
SNP	single nucleotide polymorphism
SPR	Summer Program Review
SRP	Scientific Review Program
STD	sexually transmitted disease
STTR	Small Business Technology Transfer Grant
TB	tuberculosis
TDRU	Tropical Disease Research Unit
TEAC	Technology Evaluation Advisory Committee
TMRC	Tropical Medicine Research Center
TMRU	Tropical Medicine Research Unit
UNOS	United Network for Organ Sharing
USAID	U.S. Agency for International Development
USJCMSP	U.S.-Japan Cooperative Medical Science Program
VEE	Venezuelan equine encephalitis
VRE	vancomycin-resistant enterococci
VRC	The Dale and Betty Bumpers Vaccine Research Center, NIAID
VTEU	Vaccine and Treatment Evaluation Unit
WHO	World Health Organization
WPR	Winter Policy Retreat

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